Univerzita Karlova v Praze

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MUDr. Peter Kubuš

Resynchronizace a prosynchronizace u trvalé kardiostimulace u dětí

Resynchronization and prosynchronization in permanent cardiac pacing in children

Disertační práce

Školitel: Prof. MUDr. Jan Janoušek, PhD.

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MUDr. Peter Kubuš

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Obsah

1. Abstrakt

Cíl: Zhodnocení dlouhodobých výsledků trvalé epikardiální stimulace a klinického vlivu elektromechanické dyssynchronie u trvalé kardiostimulace v dětském věku. Nalezení optimálních stimulačních míst k zamezení vzniku stimulací indukované kardiomyopatie.

Metody: Retrospektivní observační studie zaměřená na dlouhodobé výsledky trvalé epikardiální kardiostimulace u dětí v České republice. Průřezová multicentrická studie na zhodnocení dlouhodobého efektu stimulačních míst v pravé (PK) a levé (LK) komoře na mechanickou synchronii a funkci LK u dětí se strukturálně normálním srdcem vyžadujících trvalou antibradykardickou stimulaci.

Výsledky: Celková pravděpodobnost setrvalé epikardiální stimulace (absence nutnosti konverze na transvenózní stimulační systém) u dětí byla 92,8/76,1 % po 5/10 letech stimulace. Dyssynchronní srdeční selhání se nevyskytlo u žádného z pacientů iniciálně stimulovaných ze systémové komory. Místo komorové stimulace bylo jediným významným ($P < 0,0001$) prediktorem frakce zkrácení a ejekční frakce (EF) LK. Stimulace z hrotu a laterální stěny LK byla spojena se zachováním funkce LK (EF LK ≥ 55 %; poměr šancí/odds ratio (OR) = 8,26; $P = 0,018$). Stimulace výtokového traktu/laterální stěny PK byla jediným významným prediktorem snížené funkce LK (EF LK < 45 %; OR = 10,72; $P = 0,005$).

Závěr: Pravděpodobnost trvání epikardiální stimulace je u dětí vysoká a účinně odsouvá nutnost transvenózní stimulace do vyššího věku. Chronická stimulace PK, zejména její volné stěny a výtokového traktu, je spojena s vyšším rizikem rozvoje dysfunkce LK v důsledku elektromechanické dyssynchronie. Stimulace hrotu a laterální stěny LK vede k zachování funkce LK a prevenci vzniku stimulací indukované kardiomyopatie.

Klíčová slova: trvalá kardiostimulace, děti, elektromechanická dyssynchronie, stimulací indukovaná kardiomyopatie, srdeční resynchronizace

Abstract

Objectives: To evaluate the results of permanent epicardial pacing and clinical impact of electromechanical dyssynchrony in permanent cardiac pacing in children; to identify the pacing sites with the greatest potential to prevent pacing-induced cardiomyopathy.

Methods: Retrospective observational study of long-term results of permanent epicardial pacing in children in the Czech Republic. Multi-centre cross-sectional study on long-term effects of the site of ventricular pacing on left ventricular (LV) synchrony and function in children with structurally normal heart, requiring permanent pacing.

Results: Overall probability of continued epicardial pacing (absence of change to a partial or total transvenous system) was 92.8 and 76.1% at 5 and 10 years after implantation, respectively. None of those patients who were paced from the systemic ventricle developed dyssynchronous systemic ventricular failure. Pacing site was the only significant predictor of LV ejection fraction (EF) and LV shortening fraction ($P < 0.0001$ for both). Pacing from the LV apex/LV midlateral wall was associated with preserved LV function (LV ejection fraction ≥ 55%; odds ratio (OR) = 8.26; $P = 0.018$). Pacing from the RV outflow tract/lateral RV predicted significantly decreased LV function (LV ejection fraction < 45%; OR = 10.72; $P = 0.005$).

Conclusion: Permanent epicardial pacing in children has a favorable outcome in terms of pacing system survival probability and defers transvenous pacing into a significantly higher age. Right ventricular pacing sites (especially outflow tract/lateral wall) have the highest negative impact on LV electromechanical synchrony and pump function. Left ventricular

apex and lateral wall pacing preserves LV function while minimizing the risk of pacing-induced cardiomyopathy.

Key words: permanent cardiac pacing, children, electromechanical dyssynchrony, pacing-induced cardiomyopathy, cardiac resynchronization

2. Literární úvod

Trvalá kardiostimulace, která je konvenčně aplikována ze subpulmonální (zpravidla anatomicky pravé) komory, ovlivňuje negativně aktivační sekvenci komor a je nejčastější příčinou dyssynchronie systémové (zpravidla levé) komory a indikací k srdeční resynchronizační léčbě (SRL) u dětí a mladistvých. V dosavadních studiích byla opakovaně zdůrazněna nutnost tzv. prosynchronizační strategie při konvenční kardiostimulaci u dětí, tedy snahy aktivně předcházet rozvoji dysfunkce systémové komory spojené s její dyssynchronní aktivací. V rámci snah o identifikaci stimulačních míst, které by byly vhodnou alternativou k pravokomorové stimulaci, byl v několika malých akutních a střednědobých studiích prokázán příznivý vliv stimulace levé komory (LK) na zachování její elektrické i mechanické synchronie a systolické funkce. Hlavními nedostatky dosud publikovaných prací byly jednak nízký počet zahrnutých subjektů, spojený s omezenou možností hodnocení potenciálních rozdílů mezi různými stimulačními místy, jednak zahrnutí pacientů se strukturálním srdečním onemocněním, které samo o sobě může negativně ovlivnit funkci komor. Dalším faktorem, který rovněž nemohl být v dostatečné míře hodnocen, je dlouhodobý vliv kardiostimulace na funkci systémové komory.

2.1. Fyziologická elektrická aktivace srdečních komor

Správná aktivace komor, v součinnosti s jejich koordinovanou mechanickou kontrakcí a relaxací, umožňuje srdci vykonávat fyziologickou funkci pumpy k zajištění plicní a systémové cirkulace. Za fyziologických podmínek je impuls, vznikající v sinoatriálním uzlu, veden přes svalovinu síní, atrioventrikulární (AV) uzel, Hisův svazek, Purkyňova vlákna a simultánně aktivuje pracovní myokard obou komor. Téměř synchronní aktivace myokardu

prostřednictvím převodního systému srdečního vede ke koordinované mechanické kontrakci kardiomyocytů jednotlivých srdečních oddílů. Systém pravého a levého raménka včetně jejich větvení je elektricky izolován od přiléhajícího myokardu, do kterého impuls vstupuje ve spodní čtvrtině pravé komory (PK) a spodní třetině LK,[1] tedy v místech, kde byla experimentálně prokázána nejčasnější aktivace komorové svaloviny.[2-5] Aktivace interventrikulárního septa (IVS) postupuje převážně od hrotu k bázi.[5,6] Rovněž volná stěna PK a LK je aktivována od hrotu k bázi a směrem od endokardu k epikardu.[5,7,8] Posterobazální oblast je tedy nejpozději aktivovanou oblastí komorové svaloviny. Elektrický impuls je v rámci pracovního myokardu veden asi 4x pomaleji (0,3-1 m/s) než v převodním systému.[4,8,9] Celkové trvání aktivace komor se u člověka pohybuje v rozmezí 62-80 ms.[5]

2.2. Abnormální elektrická aktivace srdečních komor

K dyssynchronní aktivaci myokardu komor dochází při postižení částí převodního systému srdečního (blokáda pravého či levého raménka),[10] v přítomnosti přídatné síňokomorové spojky (komorová preexcitace charakteru Wolff – Parkinson - White)[11] nebo v případě ektopického impulsu vznikajícího při komorových extrasystolách či v průběhu komorové stimulace.[1]

Mapování mechanické aktivace komorové svaloviny při stimulaci z hrotu PK prokázalo relativně rychlou aktivaci IVS s významně opožděnou aktivací volné stěny LK,[12] pravděpodobně v důsledku pomalého transseptálního vedení impulsu.[13] Některými autory je stimulace hrotu PK užívána jako modelová situace „experimentální blokády levého Tawarova

raménka“ díky podobné morfologii QRS komplexu na povrchovém EKG. Při stimulaci z oblasti volné stěny LK naopak dochází k opožděné aktivaci IVS.

Synchronie a sekvence aktivace myokardu při komorové stimulaci je negativně ovlivněna pomalým vedením impulsu z místa stimulace přes pracovní myokard mimo převodní systém.[14-16] Výsledkem je méně synchronní aktivace komor, než při sinusovém rytmu, případně při stimulaci síní. Vzhledem k anatomickému uspořádání svalových vláken ve svalovině komor je prostorová orientace aktivační vlny dále ovlivněna skutečností, že její vedení je rychlejší ve směru podélném se svalovými vlákny než ve směru příčném,[17] a je rovněž rychlejší v subendokardiální vrstvě komorové svaloviny.[18]

Ektopický vznik impulsu v kombinaci s jeho pomalým vedením přes pracovní myokard tedy vede k dyssynchronní aktivaci komor s časnou aktivací kardiomyocytů v oblasti přiléhající k místu vzniku impulsu a opožděnou aktivací kardiomyocytů ve vzdálenějších oblastech. Ve fázi časné systoly, kdy dochází ke kontrakci časně aktivovaných oblastí, dochází k pasivnímu napětí (stretch) pozdně aktivovaných částí komorové svaloviny. Následná kontrakce těchto pozdně aktivovaných oblastí je díky jejich časně systolickému napětí (pre-stretching) relativně silnější (Frank-Starlingův mechanismus). Dyssynchronní elektrická aktivace tedy v důsledku vede k dyssynchronní mechanické kontrakci komorové svaloviny spojené se snížením globální systolické funkce komory a redistribucí mechanické práce v rámci komorové svaloviny.

S redistribucí mechanické práce dochází k regionálním změnám tkáňové perfuze,[19-21] vychytávání glukózy,[22] spotřeby kyslíku myokardem,[20] histopatologickým změnám[23] a vzniku asymetrické hypertrofie komory. Tyto změny se dále (kromě výše uvedeného Frank-Starlingova mechanismu) mohou podílet na výsledné síle kontrakce myokardu.[19,20,24,25]

V porovnání se sinusovým rytmem či stimulací síní dochází v časně aktivovaných segmentech k redukci lokální perfuze a spotřeby kyslíku až o 30 %, v pozdně aktivovaných oblastech naopak ke zvýšení obou parametrů až o 30 %.[19,20]

2.3. Vliv stimulace z pravé komory na funkci levé komory

V průběhu prvních desetiletí rozvoje klinické kardiostimulace byla věnována velká pozornost vývoji systémů s dlouhodobě stabilními elektrickými parametry (stimulační práh, snímání vlastní srdeční aktivity aj.) a systémů umožňujících zachování atrioventrikulární synchronie (dvoudutinové kardiostimulátory). Pravá komora je tradičním místem stimulace srdce vzhledem k možnosti transvenózního přístupu, případně pro svou relativně snadnou přístupnost (hrot a volná stěna PK vč. výtokového traktu) při chirurgické (epikardiální) implantaci.

Aktivace komorové svaloviny při stimulaci PK je charakterizována časnou aktivací PK a IVS s opožděnou aktivací laterální stěny LK. Výsledkem je elektrická a mechanická dyssynchronie jak mezi komorami (interventrikulární dyssynchronie), tak v rámci komor (intraventrikulární dyssynchronie). Časná aktivace PK vede k dřívějšímu nárůstu nitrokomorového tlaku v PK s následným vyklenutím IVS do LK (paradoxní pohyb IVS). Časná kontrakce IVS vzniká v době, kdy je tlak v LK nízký, a nevede tedy k ejekci. Pozdní kontrakce laterální stěny LK vzniká za podmínek zvýšeného napětí stěny a vede k opačnému paradoxnímu vyklenutí časně se kontrahujících (a zároveň předčasně relaxujících) segmentů (IVS). V důsledku toho dochází ke snížení systolické funkce LK, zvýšení end-diastolického objemu LK, zvýšení napětí volné stěny LK a její opožděné relaxaci.[26,27] Výsledná mechanická

dyssynchronie může vést ke strukturální remodelaci svaloviny komory s její dilatací,[28] rozvoji mitrální regurgitace a vzniku asymetrické hypertrofie myokardu,[28,29] které spolu s histologickými změnami,[25,30] zvýšenou myokardiální koncentrací katecholaminů[31] a regionální poruchou perfuze[21] vedou k rozvoji tzv. dyssynchronní kardiomyopatie[1,32,33] a v konečném důsledku k vyšší morbiditě a mortalitě pacientů s chronickou kardiostimulací z PK.[34-36]

Časná aktivace IVS vedoucí k jeho vyklenutí do dutiny LK[37] spolu s opožděnou kontrakcí papilárních svalů (v důsledku pomalého transseptálního vedení impulsu)[13] při stimulaci z hrotu PK se může podílet, vedle dilatace levé komory a mitrálního prstence, na vzniku mitrální regurgitace.

Prinzen[24] studiem lokální deformace myokardu (strain, změna délky svalového vlákna oproti výchozí hodnotě na konci diastoly) zjistil, že v místě komorové stimulace dochází k rychlému začátku zkracování svalových vláken (negativní strain) v časné fázi systoly, následovaným krátkým pasívním napětím (rebound stretch) a druhou fází zkrácení. V místech vzdálených stimulačnímu bodu dochází k významnému pasívnímu časně systolickému napětí (stretch) následovaným zkrácením v době ejekční fáze. Charakter těchto změn se mění kontinuálně od místa stimulace ke vzdálenějším segmentům.[19] V segmentech blízkých stimulačnímu místu dochází v časné fázi systoly částečně k pasivní deformaci, a tyto segmenty vykonávají z energetického hlediska negativní práci, jak vyplývá z analýzy křivek zobrazujících vztah mezi mírou napětí a relativní změnou délky svalového vlákna (fiber stress – fiber length loops). Tyto křivky byly použity pro posouzení lokálně vynaložené práce jako analogie tlakově-objemovým křivkám používaným pro srdeční komoru jako celek (u kterých plocha vymezená křivkou na tlakově-objemovém diagramu odpovídá celkové mechanické

práci vynaložené komorou na srdeční stah a je součtem potenciální [udržení stálého napětí/tonusu srdeční svaloviny] a externí [kinetické] práce vykonané myokardem). Takto definovaná externí práce dosahovala negativních hodnot v místech blízkých stimulaci a naopak „supranormálních“ hodnot v místech vzdálených. Oblast myokardu vykonávající sníženou externí práci byla rozsáhlejší při stimulaci z hrotu PK než při stimulaci báze LK (u které nebyly patrné významné rozdíly oproti stimulaci síní se spontánní aktivací komor přes převodní systém). Výsledné snížení tepového objemu je úměrné počtu hypofunkčních segmentů přiléhajících k místu stimulace. Jak již bylo uvedeno, lokálním změnám vynaložené práce odpovídají změny regionální perfuze, spotřeby kyslíku myokardem[19,20] a rozvoj asymetrické hypertrofie[28,29] myokardu. V případě stimulace z hrotu PK je místem snížených metabolických nároků časně aktivované interventrikulární septum, k hypertrofii svaloviny naopak dochází v opožděně aktivované laterální stěně LK.[28,29] Popsané změny regionální perfuze a charakteru kontrakce jsou úměrné frekvenci[21]a trvání[38] abnormální aktivace (stimulace).

Adomian a spol. (1986) v experimentu na zvířatech popsal abnormální změny myofibril po několika měsících stimulace hrotu PK, pravděpodobně v souvislosti s abnormální aktivační sekvencí srdeční svaloviny (sekvence depolarizace) a s ní spojenou změnou charakteru srdeční kontrakce.[30] Karpawich (1999) popsal histopatologické změny u dětských pacientů s konvenční kardiostimulací z PK pro kongenitální atrioventrikulární blokádu, mj. variace velikosti svalových vláken, fibrotické a sklerotické změny, tuková depozita a morfologické změny mitochondrií.[23] Zvýšená intersticiální fibrotizace a fragmentace myofibril byla pozorována v oblasti volné stěny LK při stimulaci hrotu PK.[39] Na buněčné úrovni byla pozorována redistribuce některých molekul v pozdně aktivovaných segmentech myokardu (přesun connexinu43, proteinu lokalizovaného do interkalárních disků, směrem

k laterální membráně kardiomyocytů).[40] Nerovnoměrné zatížení komorové svaloviny v důsledku dyssynchronie vede k lokálním změnám exprese/aktivity molekul spojených s metabolismem kalcia a procesem apoptózy (např. zvýšená exprese TNF-α [tumor necrosis factor-α] v pozdně se kontrahujících segmentech, zvýšená aktivita kaspázy 3, snížená aktivita Akt kinázy).[41] Celulární remodelace při stimulaci PK je doprovázena změnami v extracelulární matrix (zvýšená aktivita MMP-9 [metaloproteináza-9] jak v interventrikulárním septu, tak v pozdně aktivované laterální stěně LK, zvýšená aktivita MMP-2 a tkáňových inhibitorů metaloproteináz [TIMP-1, TIMP-3] v laterální stěně LK)[39] a rovněž změnami plazmatické koncentrace specifických proteinů podílejících se na procesu apoptózy (annexin A5, protein ovlivňující permeabilitu stěny mitochondrií a inhibující proteinkinázu C). Snížení koncentrace annexinu A5 bylo naopak pozorováno po zahájení srdeční resynchronizační terapie.[42]

Řada studií prokázala potenciálně nepříznivý vliv komorové stimulace na relaxaci komorové svaloviny, zejména ve fázi izovolumické relaxace.[43-45] Stimulace komor z různých míst vedla k podobnému stupni poruchy kontrakce a relaxace myokardu ve sledovaných oblastech.[44] Porucha synchronie kontrakce je tedy pravděpodobně spojena s poruchou synchronie relaxace. Synchronní aktivace komor, spojená s větším tepovým objemem, vede k menšímu end-diastolickému objemu komory a rychlejší relaxaci komorové svaloviny.[46]

2.4. Vliv atrioventrikulární sekvenční stimulace a místa stimulace na funkci levé komory

Při jednodutinové komorové stimulaci a absencí AV synchronie dochází v průběhu jednotlivých srdečních stahů k měnlivému příspěvku síní v době diastolického plnění komor, jehož odrazem je mj. měnlivý systolický objem a systolický tlak.[47] Zavedení dvoudutinové (AV

sekvenční) stimulace vedlo ke zlepšení hemodynamických parametrů v experimentech se zvířaty[48] i v souborech pacientů,[49] a to zejména po optimalizaci AV intervalu.[49,50]

Vzhledem ke skutečnosti, že sekvenční dvoudutinová kardiostimulace se zachovanou AV synchronií vedla k lepšímu zachování systolické funkce LK v porovnání s komorovou stimulací samotnou,[48,49] byla abnormální aktivace komor v počátcích rozvoje trvalé kardiostimulace považována za relativně méně důležitou. Kosowsky a spol. (1968) poukázali na význam sekvence aktivace komorové svaloviny porovnáním stimulace z hrotu PK se stimulací z oblasti Hisova svazku při zachování možnosti měnit AV interval.[51] Daggett a spol. (1970) prokázali lepší systolickou funkci LK při stimulaci z LK v porovnání se stimulací z PK.[48] Řada následných studií s použitím výlučně komorové[14,52] nebo AV sekvenční[19,36] stimulace prokázala významný vliv místa stimulace na systolickou funkci LK. Při hledání alternativních míst pro stimulaci bylo zjištěno, že stimulace ze septální části výtokového traktu PK vede ke zlepšení synchronie kontrakce a systolické funkce LK v porovnání se stimulací z hrotu PK,[53] ačkoli konfigurace a trvání QRS komplexu byla nadále abnormální v porovnání se sinusovým rytmem či stimulací síní samotnou.

V posledních letech, mj. v souvislosti s vývojem nových stimulačních elektrod s možností zavedení transvenózně do koronárního sinu, významně přibývá evidence týkající se zlepšení funkce LK u pacientů se srdečním selháním (a poruchou vedení vzruchu) po zavedení simultánní stimulace PK a LK (biventrikulární stimulace), případně stimulace z LK samotné.[54,55] Při porovnání různých míst na LK vedla stimulace z hrotu LK při absenci nativní levokomorové dyssynchronie k nejlepším výsledkům ve smyslu zachování její systolické funkce.[56]

2.5. Prevence stimulací indukované dyssynchronie

Smyslem kardiostimulace u pacientů s AV blokádou a bradykardií je zvýšení resp. normalizace tepové frekvence, které samy o sobě vedou ke zvýšení srdečního výdeje v porovnání s pomalými frekvencemi komor při AV blokádě.[47] Kardiostimulace u těchto pacientů zároveň snižuje riziko náhlé srdeční smrti v důsledku asystolie a riziko selhání LK při neléčené AV blokádě v důsledku bradykardie.[57] Přítomnost AV blokády je tedy zejména u pacientů se symptomatickou bradykardií jednoznačnou indikací k zavedení trvalé kardiostimulace.[58] Konvenční stimulace z PK je však spojena s dyssynchronní elektrickou aktivací komor vedoucí k mechanické dyssynchronii jejich kontrakce a potenciálně k rozvoji dysfunkce systémové komory s její patologickou remodelací a zvýšenému riziku srdečního selhání. Kim[59] ve studii zahrnující 63 dětí s trvalou stimulací z PK pro úplnou atrioventrikulární blokádu zjistil echokardiografické známky dysfunkce LK u 10 % pacientů stimulovaných > 10 let, přičemž faktory asociovanými se sníženou systolickou funkcí LK byly stimulace z hrotu PK a trvání QRS komplexu. Gebauer[60] v souboru dětských pacientů stimulovaných z PK popsal snížení hodnoty frakčního zkrácení v průběhu dlouhodobé kardiostimulace, přičemž kombinaci dilatované LK a nižší hodnoty frakčního zkrácení nalezl u 13,4 % pacientů (11/82 pacientů, klinické příznaky srdečního selhávání byly přítomny u 8/11 pacientů). Epikardiální stimulace z volné stěny PK byla v této studii identifikována jako nezávislý rizikový faktor pro rozvoj dilatace a dysfunkce LK v průběhu dlouhodobé kardiostimulace.

Při stimulaci z laterální stěny LK dochází k aktivaci této části komory před aktivací IVS a volné stěny PK, k zamezení paradoxního pohybu IVS v časné fázi systoly a lepší systolické funkci LK než při stimulaci z PK.[37] Stimulace z hrotu LK se rovněž více blíží fyziologické

sekvenci aktivace komor směrem od srdečního hrotu k bázi.[61] Akutní zvýšení systolické funkce LK při stimulaci z hrotu LK v porovnání se stimulací z hrotu PK bylo zaznamenáno u dětí bezprostředně po kardiochirurgickém výkonu.[55] Stimulace z LK u pacientů vedla v některých studiích k podobnému zlepšení funkce LK jako při biventrikulární stimulaci.[62,63,64] Významné zlepšení funkce a zmenšení dilatace LK byly popsány po změně místa stimulace na LK u dětí se srdečním selháním indukovaným chronickou stimulací z PK.[65]

2.6. Srdeční resynchronizační léčba

Srdeční resynchronizační léčbou (SRL) rozumíme stimulaci srdce cílenou na dosažení synchronní aktivace komor. Prostřednictvím řízené stimulace myokardu (dříve než se uplatní abnormální vlastní vedení impulsu) tak lze snížit nežádoucí dyssynchronii kontrakce komor. Klinický význam SRL byl popsán již v r. 1994.[66] V praxi je SRL nejčastěji dosaženo pomocí biventrikulární stimulace. Její příznivý vliv u pacientů se srdečním selháním na podkladě idiopatické či ischemické kardiomyopatie s dyssynchronií systémové komory zapříčiněné blokádou levého Tawarova raménka nebo trvalou kardiostimulací z PK byl popsán v řadě klinických studií.[67-72] SRL byla doporučena jako přídatná terapie u vybraných pacientů se srdečním selháním v r. 2002.[73-75] Biventrikulární stimulace zlepšuje funkci LK a vede k její reverzní remodelaci včetně celulární úrovně,[76-78] zlepšuje klinický stav a snižuje mortalitu u pacientů s významnou dysfunkcí LK a klinickými známkami srdečního selhání. Biventrikulární stimulace je jednoznačně doporučena (indikační třída I) u pacientů s blokádou levého Tawarova raménka (QRS > 150 ms), ejekční frakcí LK ≤ 35 %, kteří jsou ve třídě II, III, nebo [ambulantní pacienti] IV dle funkční klasifikace NYHA (New York Heart Association) přes zavedenou adekvátní farmakologickou léčbu.[79,80]

Využití SRL v dětském věku bylo popsáno ve třech větších[81-83] studiích limitovaných nejen počtem pacientů, ale také jejich retrospektivním charakterem. Významným faktorem limitujícím možnost prosté extrapolace dat ze studií u dospělých je výrazná heterogenita dětské populace s početným zastoupením pacientů se strukturální vrozenou srdeční vadou, mnohdy se systémovou pravou nebo funkčně společnou komorou, zpravidla po různých kardiochirurgických výkonech. Dubin a spol. (2005) v multicentrické studii zahrnující 103 pacientů (medián věku 12,8 [rozmezí 0,3-55,4] roku, medián sledování 4 měsíce) popisují významný nárůst EF LK ze 26,2 ± 11,6 % na 39,9 ± 14,8 %, bez významných rozdílů mezi podskupinami pacientů (kardiomyopatie, kongenitální kompletní AV blokáda, pacienti se strukturální vrozenou srdeční vadou).[83] Janoušek a spol. upozornili na skutečnost, že spektrum dětských pacientů podstupujících SRL se významně liší od dospělé populace.[81] V jejich studii byli pacienti se systémovou levou komorou a blokádou levého Tawarova raménka (nejčastější skupina v dospělé populaci) zastoupeni pouze v 9 %. Nejpočetnější skupinu (77 %) tvořili pacienti s předchozí konvenční kardiostimulací z PK. Práce definovala rizikové faktory pro neefektivitu SRL, jimiž byly primárně dilatační kardiomyopatie a vyšší třída NYHA klasifikace (medián NYHA III u non-responderů SRL oproti NYHA II u responderů). Nejlepší odpovědi na SRL bylo naopak dosaženo u pacientů s předchozí konvenční kardiostimulací z PK. Efektivita SRL u dětí je tedy závislá na typu strukturálního a patofyziologického substrátu. NYHA třída korelovala s parametry systolické funkce systémové komory pouze omezeně a je otázkou, do jaké míry by nadále měla patřit mezi hlavní indikační kritéria k zavedení SRL v dětském věku a u pacientů se strukturální srdeční vadou. SRL by v této skupině pacientů pravděpodobně měla být zvažována proaktivněji již při přítomnosti mírnější dysfunkce systémové komory spojené s dyssynchronií, zejména

(vzhledem k nízkému věku) s ohledem na ochranu před rozvojem srdečního selhání a poškozením myokardu.

3. Cíle disertační práce

1. Zhodnocení dlouhodobých výsledků trvalé epikardiální stimulace v dětském věku

2. Zhodnocení klinického vlivu elektromechanické dyssynchronie u trvalé kardiostimulace v dětském věku

3. Nalezení optimálních stimulačních míst pro trvalou kardiostimulaci u dětí ve smyslu zachování synchronie a funkce levé komory a minimalizace rizika stimulací indukované kardiomyopatie

4. Hypotézy

1. Permanentní epikardiální stimulace umožňuje v dětském věku efektivně odsunout nutnost transvenózní stimulace a zachovat tak průchodný žilní systém pro budoucí endovazální implantace.

2. Nalezením vhodného místa pro trvalou stimulaci komor u dětí lze významným způsobem omezit riziko stimulací indukované kardiomyopatie, která vzniká v důsledku elektromechanické dyssynchronie při konvenční stimulaci ze subpulmonální komory a v dětském věku je nejčastější indikací k srdeční resynchronizační léčbě.

5. Výsledky

Následující část disertační práce se věnuje zhodnocení výsledků dlouhodobé epikardiální stimulace u dětí, klinického významu elektromechanické dyssynchronie a identifikaci optimálních stimulačních míst pro trvalou kardiostimulaci u dětí ve smyslu zachování synchronie a funkce levé komory a minimalizace rizika stimulací indukované kardiomyopatie.

Součástí tohoto oddílu jsou 4 publikované klinické studie.

1. Permanent epicardial pacing in children: long-term results and factors modifying outcome

Souhrn

V retrospektivní observační studii byly hodnoceny dlouhodobé výsledky trvalé epikardiální stimulace v dětském věku s ohledem na výskyt dlouhodobých komplikací ve smyslu přežívání komponent stimulačního systému. Do studie bylo zahrnuto všech 119 (období 1977 – 2009) konsekutivních pacientů (věk při implantaci < 18 let, medián 1,8 roku) z České republiky. Použití elektrod s postupným uvolňováním steroidů snížilo riziko exit bloku (poměr rizik/hazard ratio [HR] = 0,20, 95% interval spolehlivosti (CI) 0,09 – 0,44, P < 0,001). Využití specifické programovatelné funkce automatického měření stimulačního prahu AutoCapture™ (HR = 0,08, 95% CI 0,02 – 0,36, P < 0,001) a steroidních elektrod (HR = 0,30, 95% CI 0,11 – 0,84, P = 0,021) snížilo riziko vyčerpání generátoru. Používání steroidních elektrod a funkce AutoCapture™ tak v konečném důsledku vedlo k významnému zvýšení životnosti stimulačního systému a snížení nutnosti chirurgické reintervence. Celková pravděpodobnost setrvalé epikardiální stimulace byla 76,1 % po 10 letech kardiostimulace, zvýšila se v posledních letech sledovaného období (po r. 2000, P = 0,040) a umožnila odsunout nutnost transvenózní stimulace do významně vyššího věku. Žádný z pacientů nezemřel z důvodu selhání stimulačního systému.

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CLINICAL RESEARCH

Permanent epicardial pacing in children: long-term results and factors modifying outcome

Petr Kubuš[1]*, Ondřej Materna[1], Roman A. Gebauer[2], Tomáš Matějka[1], Roman Gebauer[1], Tomáš Tláskal[1], and Jan Janoušek[1]

[1]Kardiocentrum and Cardiovascular Research Centre, University Hospital Motol, V Úvalu 84, 150 06 Prague, Czech Republic; and [2]Department of Paediatric Cardiology, University of Leipzig, Heart Centre, Strümpellstrasse 39, 04289 Leipzig, Germany

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Aims To evaluate the results of permanent epicardial pacing in children.

Methods and results All consecutive patients from one country ($n = 119$, period 1977–2009) undergoing permanent epicardial pacemaker implantation at <18 years of age (median 1.8 years, inter-quartile range 0.3–6.4 years) were studied retrospectively. Median patient follow up was 6.4 years (inter-quartile range 2.9–11.1 years); 207 generators, 89 atrial and 153 ventricular pacing leads were implanted. The probability of absence of any pacing system dysfunction was 70.1 and 47.2% at 5 and 10 years after implantation, respectively. Overall probability of continued epicardial pacing was 92.8 and 76.1% at 5 and 10 years, respectively, and increased in the recent implantation era (post-2000, $P = 0.04$). The use of steroid-eluting leads decreased the risk of exit block with a hazard ratio (HR) of 0.20 [95% confidence interval (CI) 0.09–0.44, $P < 0.001$)]. The use of bipolar Medtronic 4968 leads reduced the risk of surgical reintervention because of fracture, insulation break, outgrowth or exit block in comparison to the unipolar 4965 lead design (HR 0.12, 95% CI 0.04–0.40, $P < 0.001$). The AutoCapture™ feature (HR 0.08, 95% CI 0.02–0.36, $P < 0.001$) and steroid-eluting leads (HR 0.30, 95% CI 0.11–0.84, $P = 0.021$) decreased the risk of battery depletion.

Conclusion The probability of continued epicardial pacing in children was 76% at 10 years after implantation, increased for implantation in recent years, and allowed transvenous pacing to be deferred to a significantly greater age. The use of bipolar steroid-eluting leads and of a beat-to-beat capture tracking feature significantly increased pacing system longevity and decreased the need for surgical reinterventions.

Keywords Pacing • Epicardial • Children • Atrioventricular block • Congenital heart disease

Introduction

The approach to permanent cardiac pacing in children is determined by specific issues related to age and physical growth, presence of structural congenital heart disease, limited venous access to the heart, risk of venous thrombosis, choice of optimal pacing site to prevent pacing-induced dyssynchronous cardiomyopathy, and the perspective of pacing for decades. The aim of this population-based study was to evaluate long-term results of permanent epicardial pacing in children and to determine factors modifying pacing system survival.

Methods

Patients

The study population was identified retrospectively from the clinical database of a single nationwide tertiary care centre providing paediatric pacemaker therapy for the whole territory of the Czech Republic (10.5 million inhabitants). One hundred and nineteen consecutive patients (56 boys and 63 girls) with epicardial pacemaker implantation at <18 years of age between 1997 and 2009 were included. These patients represented a subgroup of a total of 245 paediatric pacemaker recipients over the same time period (*Figure 1A* and *B*). The median age

* Corresponding author. Dětské kardiocentrum, Fakultní nemocnice v Motole, V Úvalu 84, 150 06, Prague, Czech Republic. Tel: +00420 22443 2901; fax: +00420 22443 2914.
Email: peter.kubus@lfmotol.cuni.cz

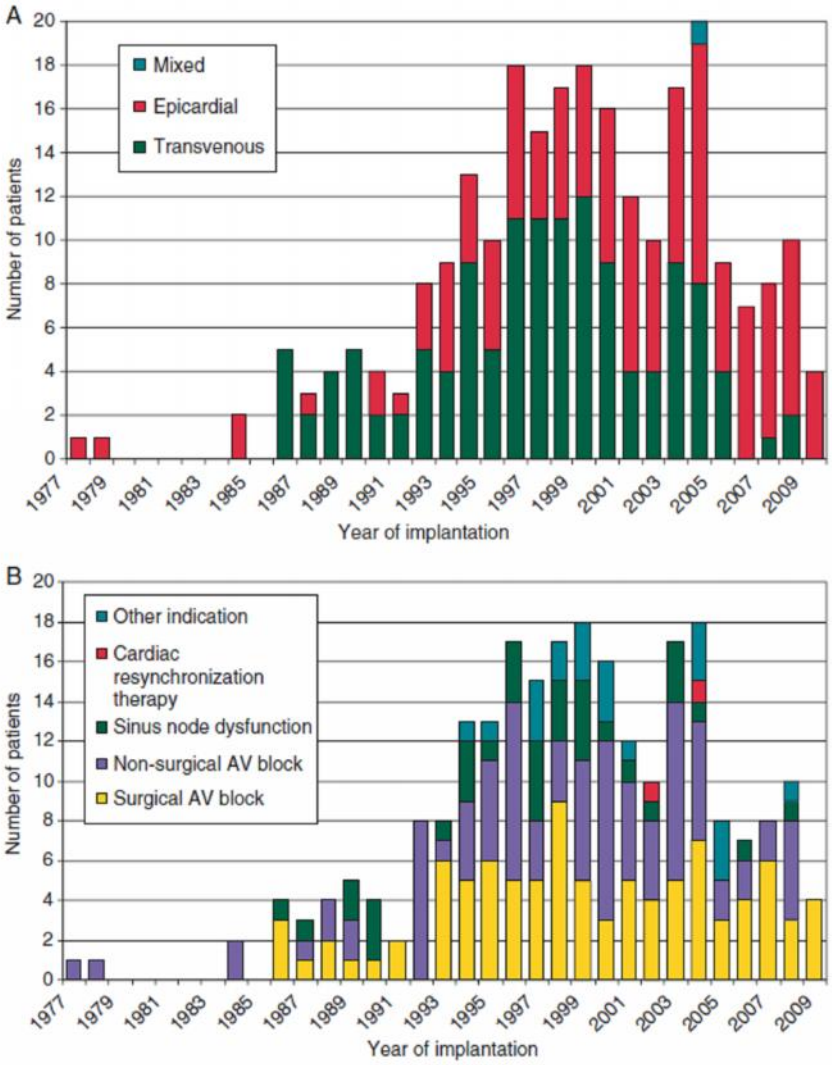

Figure 1 (*A*) Frequency and type of pacemaker primary implantations during the study period. (*B*) Indications for pacemaker implantation.

at implantation was 1.8 years [inter-quartile range (IQR) 0.3–6.4 years] and median weight 10.0 kg (IQR 4.5–19.8 kg). Except for five patients with previous transvenous pacing, all had undergone their first pacing system implantation. Patients with mixed systems (transvenous and epicardial leads) were excluded. Structural congenital heart disease was present in 91 (76.5%) patients. The systemic ventricle was morphologically left in 81 of 119, right in 19 of 119 and single in 19 of 119 patients. The indication for pacing was second or third degree atrioventricular (AV) block in 103 (86.6%; surgical in 60 of 103 patients), sinus node dysfunction in 12 (10.1%), bradycardia–tachycardia syndrome in 2 (1.7%), breath-holding spells with asystole in 1 (0.8%), and first degree AV block with a right bundle branch block in 1 patient (0.8%). Patients were followed up for a median of 6.4 years (IQR 2.9–11.1 years) after the implantation. There were 48 patients with a primary epicardial pacing system implantation in the early era (defined as pre-2000) and 71 patients in the recent era (2000–2009). None of patients has been lost to follow up.

Pacing system

The initial pacing system was single-chamber atrial (AAI/R) in 5 patients (4.2%), ventricular (VVI/R) in 39 (32.8%), dual-chamber in 64 (53.8%, DDD/R = 57, VDD = 2 and DDI = 5) and biventricular in 11 patients (9.2%, all in dual-chamber pacing mode). Altogether, 207 pulse generators were used during primary implantation and replacement procedures. A total of 89 atrial and 153 ventricular leads placed on either the subpulmonary ($n = 92$) or the systemic ventricle ($n = 61$) were implanted during the study period. Of these leads, 166 (68.6%) were bipolar and 202 (83.5%) were steroid-eluting (*Table 1*). Except for two patients with a subpectoral pocket, all generators were

Table 1 Epicardial pacing leads used in the study

Lead type	Manufacturer	Steroid-elution	Polarity	Number of leads implanted
4968	Medtronic	Yes	Bipolar	161
4965	Medtronic	Yes	Unipolar	35
ML 150/160	Biotronik	No	Unipolar	16
ELC	Biotronik	No	Unipolar	10
4951	Medtronic	No	Unipolar	9
Encor	Cordis	No	Unipolar	3
10366	Medtronic	Yes	Bipolar	3
MyoDex 1084T	St Jude Medical	Yes	Bipolar	1
MX 50/02-BP	Biotronik	No	Bipolar	2
5071	Medtronic	No	Unipolar	1
V 105	Biotronik	No	Unipolar	1

placed in the subrectal abdominal position using a subxiphoid or median sternotomy approach to lead implantation.

Follow up

We performed a retrospective analysis of pacemaker records, including demographic data, surgical implantation/revision data and clinical follow-up files. For the purpose of pacing system survival analysis, pacemaker dysfunction was defined by the presence of any of the following end-points: the generator replacement and/or the lead replacement/revision/abandonment due to an exit block; a major increase in pacing threshold; a fracture or an insulation break; patient outgrowth; premature battery depletion (less than the projected minimal longevity of the generator at nominal settings minus 2 years); or an infection. Lead survival analysis was performed for all leads ($n = 242$) and separately for the most commonly used Medtronic 4968/4965 suture-on steroid-eluting bipolar/unipolar leads ($n = 196$). Generators ($n = 99$) with >90% of ventricular pacing, without a change in the ventricular lead type and with the AutoCapture™ feature either available and on ($n = 18$) or not available/off ($n = 81$) during the whole generator follow-up period were subjected to a subanalysis of factors influencing the battery longevity.

Statistical analysis

Continuous data are displayed as medians and IQR or means ± SD as appropriate according to the mode of distribution. The actuarial survival probability was computed using the Kaplan–Meier method and the log-rank statistics for the detection of differences between two groups. Risk factors for a pacing system dysfunction were evaluated using the Cox regression proportional hazards model with entry criteria for univariate $P < 0.2$. Confidence intervals (CI) at 95% are presented for hazard ratios (HR). For the purpose of epicardial pacing system survival analysis, each patient was entered once, and modelling was performed for the time to change to a transvenous system using age at the implantation, history of other cardiac surgery, patient sex, and the implantation era as independent variables. Lead-related risk factors were identified using the lead as the unit of analysis. Independent variables included age and height at the implantation, patient sex, history of other cardiac surgery, and the lead type (atrial vs. ventricular, unipolar vs. bipolar, steroid-eluting or not). The battery longevity was evaluated using the following independent variables in a multivariable risk model: age at the implantation; history of other cardiac surgery; patient sex; steroid-elution; dual-chamber pacing; AutoCapture™ feature; battery capacity; and resting battery current. Values of $P < 0.05$ were regarded as significant. All statistical analysis was performed with SigmaPlot for Windows version 11.0 (Systat Software Inc., San Jose, CA, USA).

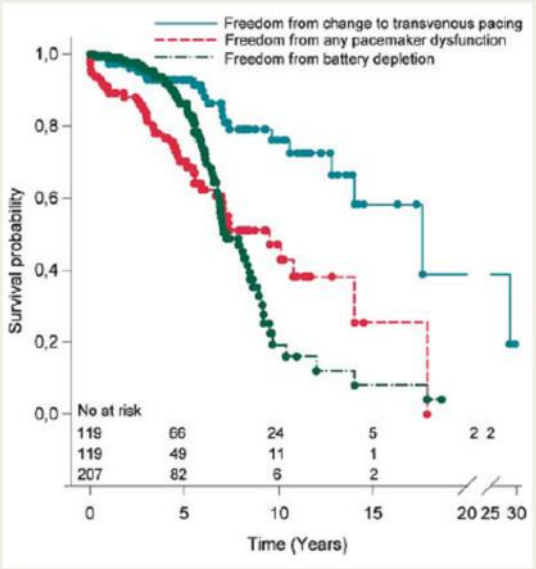

Figure 2 Epicardial pacemaker survival probability. Number of patients at risk at a particular follow-up time is displayed for the three survival curves.

Results

Pacing system survival

An overall probability of freedom from pacing system dysfunction (absence of all of the defined end-points) after the primary implantation was 70.1 and 47.2% at 5 and 10 years of follow up, respectively (*Figure 2*). Fifty-five surgical revisions were necessary over the whole study period in a total of 52 of the 119 patients (44.0%) for

the following reasons: exit block/major increase in pacing threshold ($n = 17$); lead fracture/insulation break ($n = 7$); patient outgrowth ($n = 8$); pacing system infection ($n = 6$); and premature battery depletion ($n = 17$). Another 12 complications were treated conservatively including six cases of systemic steroid administration due to a major increase in pacing threshold, pericardial effusion in four patients, and pocket haematoma in another two patients. The probability of freedom from battery depletion was 95.3, 73.4, and 32.7% at 3, 6, and 9 years, respectively (*Figure 2*). An overall probability of continued epicardial pacing (absence of change to a partial or total transvenous system) was 92.8 and 76.1% at 5 and 10 years after the implantation, respectively (*Figure 2*), and increased in the recent implantation era (2000 and later) from 71.5 to 86.8% at 9 years ($P = 0.040$). In a multivariable analysis, two factors increased and decreased the necessity of a change to a transvenous system, respectively: male sex (HR = 2.99, 95% CI 1.20–7.44, $P = 0.018$) and recent implantation era (HR = 0.26, 95% CI 0.07–0.95, $P = 0.042$). Age at the implantation had no influence.

Risk factors for lead failure

Steroid-eluting leads showed a significantly higher freedom from an exit block than non-steroid leads (95.3 vs. 76.2% at 5 years, $P < 0.001$, *Figure 3*) with a hazard ratio of 0.20 (95% CI 0.09–0.44, $P < 0.001$). The use of the bipolar Medtronic 4968 leads significantly reduced the risk for surgical reinterventions because of a fracture, an insulation break, outgrowth, or an exit block in comparison to the unipolar 4965 lead design (HR 0.12, 95% CI 0.04–0.40, $P < 0.001$; survival probability 94.0 vs. 58.3% at 8 years, $P < 0.001$). Height at the time of implantation was a further multivariable predictor (HR 0.81, 95% CI 0.67–0.98, $P =$ 0.028 per each 10 cm increment). The superiority of the bipolar lead resulted almost completely from the possibility of saving its functionality by reprogramming the generator output to unipolar configuration in the event of damage to the indifferent wire. This could be proved by a similar survival probability of the two lead designs if the necessity of the output configuration change was included as one of the lead survival end-points.

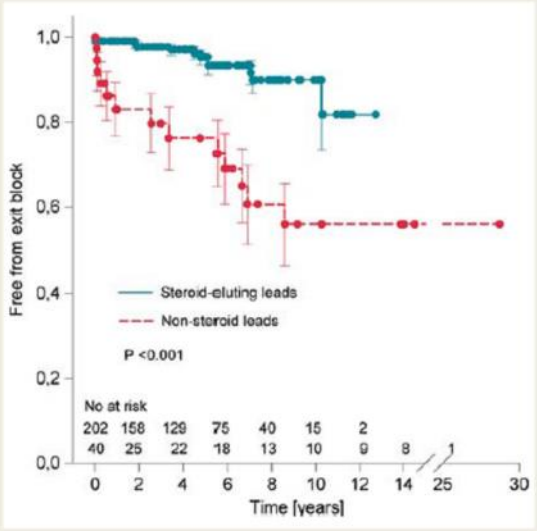

Figure 3 Probability of freedom from exit block. Number of patients at risk at a particular follow-up time is displayed for both survival curves.

Battery longevity

Factors influencing the risk of battery depletion are displayed in *Figure 4*. Of these factors, the AutoCapture™ feature (HR 0.08, 95% CI 0.02–0.36, $P < 0.001$), steroid-eluting leads (HR 0.30, 95% CI 0.11–0.84, $P = 0.021$), higher battery capacity (HR 0.05, 95% CI 0.01–0.29, $P < 0.001$), and higher resting battery current (HR 1.22, 95% CI 1.03–1.46, $P = 0.025$) are significant in terms of clinical decision making. On the contrary, the dual chamber mode did not influence battery longevity in comparison to the single chamber (VVI/R) pacing. AutoCapture™ had to be switched off for various reasons in nine generators, resulting in an increase in the battery drain due to higher output programming from 9.1 ± 2.1 to 11.8 ± 4.7 μA ($P = 0.042$).

Systemic ventricular dysfunction

A total of 10 of 77 patients (13.0%) paced initially from a single site at the subpulmonary or single ventricle showed signs of a dyssynchronous systemic ventricular failure, yielding an event-free survival probability of 90.4 and 82.1% at 5 and 10 years, respectively. They were upgraded to biventricular pacing ($n = 8$), the pacemaker was programmed off ($n = 1$), or they died from heart failure ($n = 1$). None of the 37 patients who were paced from the systemic ventricle or underwent a primary biventricular pacemaker implantation showed such a complication ($P = 0.05$ χ^2 test and = 0.08 log rank). None of the following independent variables was significantly associated with the development of dyssynchronous cardiomyopathy in an univariate analysis ($P > 0.2$ for all): presence of structural heart disease; the anatomical type of the

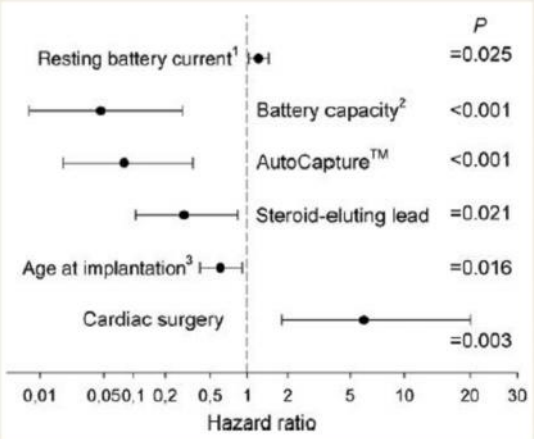

Figure 4 Factors affecting battery longevity. Explanations: [1]per microampere, [2]per ampere hour, [3]per each 5 years increment.

systemic ventricle; AV block aetiology; age at the time of implantation; pacing duration; and use of a dual-chamber pacing mode.

Death

Fourteen of the 119 (11.8%) patients died during follow up. All had structural congenital heart disease. The reasons for death were complex congenital heart disease ($n = 10$), sepsis ($n = 3$), and pacing-associated systemic ventricular failure ($n = 1$). There was no death related to the pacing system failure or an infection. The patient who died from a systemic ventricular failure underwent surgical correction of tetralogy of Fallot at the age of 1 year. Owing to a complete surgical AV block, a single chamber pacemaker in the VVI mode with an epicardial pacing lead on the right ventricular apex was implanted after the surgery. After 5.8 years of VVI pacing, exit block occurred, and a new pacing system with transvenous atrial and right ventricular apical pacing leads was implanted. The patient died after 0.8 years of dual-chamber pacing, showing signs of a progressive left ventricular failure suspicious of severe intra-left ventricular dyssynchrony on a *post hoc* analysis.

Discussion

In children, epicardial pacemaker implantation is indicated in the presence of intracardiac shunts, absence of appropriate cardiac cavity, and absent or limited venous access to the heart. Patient size is handled individually, with many institutions preferring epicardial pacing in smaller children, while others use a transvenous approach early on.[1–3] Modern steroid-eluting epicardial leads have almost eliminated the advantage of endocardial leads as far as pacing threshold and battery longevity are concerned.[2,4] Transvenous leads carry a significant risk of venous thrombosis not exclusively related to the disproportion between the pacing lead and vein diameter.[5–7] Thus, epicardial lead placement has an appealing potential for sparing the great veins in young individuals with the perspective of decades of cardiac pacing. Furthermore, new data have pointed towards the negative effect of right ventricular pacing on left ventricular synchrony and function,[8–11] as well as on preservation of left ventricular function by left ventricular apical or free wall pacing,[12–14] both necessitating an epicardial approach. On the other hand, patient safety is of concern in pacemaker-dependent individuals, with epicardial leads showing a higher risk of a fracture than transvenous electrodes.[1] The results of the present study may contribute to the clinical decision between the epicardial and transvenous approaches, touching several important aspects of paediatric pacemaker therapy.

Epicardial pacing system longevity

Despite the need for surgical reinterventions, the initial epicardial approach enabled transvenous pacing to be deferred to a significantly greater age. In the recent era, the probability of being paced epicardially reached 87% at 9 years after the implantation, which mainly reflects technical advances in lead design. Importantly, this probability was not influenced by patient age at the time of implantation. Thus, even very young patients could benefit from the epicardial approach in terms of avoidance of an early change to a transvenous system. Interestingly, male sex was a risk factor for an earlier change to a transvenous system. Whether this was caused by a more active lifestyle and sport participation remains speculative. Further factors with a positive influence on generator longevity in this study included the use of the AutoCapture™ feature, a finding in support of the previously published data on the increase in calculated battery service life,[15] and the use of steroid-eluting leads. Although it was shown in one previous report[2] that threshold energy still differs significantly between modern transvenous and epicardial steroid-eluting leads, this difference was mainly confined to the unipolar lead design, associated with a lower pacing impedance causing a higher current drain. Bipolar epicardial leads showed only a very marginal difference in threshold energies,[2] which is not likely to be significant in terms of generator survival, especially in combination with automatic threshold-tracking algorithms. Still, several factors may decrease battery longevity, such as younger age at the time of implantation and a previous cardiac surgery, reflecting faster heart rates and the presence of scarring leading to higher thresholds, respectively. Interestingly, no difference has been found between dual- and single-chamber pacing modes.

Lead failure

With the advent of steroid-eluting epicardial leads, the difference in epicardial vs. transvenous lead survival has become marginal.[1,3] This study confirmed previous findings[16,17] by showing a four-fold decrease in the risk of an exit block with the use of steroid-eluting leads. More importantly, this is to our knowledge the first report showing a better intervention-free survival of the bipolar Medtronic 4968 lead in comparison to the unipolar 4965 lead design from the same company. Both leads are currently the most commonly used electrodes for epicardial pacing in children. The superiority of the bipolar lead is probably attributed to the more robust construction design, with damage occurring predominantly in the indifferent lead wire, while leaving the more protected different wire still available for unipolar pacing after reprogramming the generator output configuration. The bipolar Medtronic 4968 lead carries more patient safety if used along with unipolar pacing or with an automatic output configuration feature, as available from several generator companies, that switches to unipolar pacing in the event of a major impedance change. Our present approach is to leave pacemaker non-dependent patients with the unipolar configuration if necessary. In dependent patients, we discuss the surgical revision options with the family, taking into account the patient's age, growth potential, lead tension, feasibility of a transvenous approach, and preference for a specific ventricular pacing site.

Systemic ventricular dysfunction

This study provides a further stone into the mosaic of our understanding of pacing-induced dyssynchronopathy. Single-site pacing from the subpulmonary or single ventricle was associated with a significant rate of systemic ventricular failure necessitating therapy, most commonly cardiac resynchronization. Such an adverse outcome was not seen with pacing from the systemic ventricle. This association confirms recent findings from other studies[8–11] on the poor tolerance of right ventricular pacing in at least a subset of paediatric patients with systemic left ventricle and the preservation of function with left ventricular pacing.

Limitations

The time period of the study is quite long; thus, changes in technology and major differences in follow-up times may have influenced the results in further indiscernible ways. Also, the number of patients with follow-up times longer than 11 years is limited and therefore decreases the validity of statistical survival projections for follow-up intervals exceeding this period. The conclusions of the study are, however, mainly based on follow-up data of up to 10 years, where enough patients at risk were available to draw significant conclusions. We also tried to overcome the limitation of hardware diversity by focusing on leads with a uniform lead design, such as the Medtronic 4968/4965 leads, in a subanalysis. This study was not specifically designed to evaluate systemic ventricular function, because many retrospective data were lacking. Thus, data on the clinical consequences of pacing-induced dyssynchronopathy could not be amended by systemic ventricular function parameters.

Clinical implications

Reflecting the results of this study, currently available steroid-eluting epicardial leads may well be used on an individual decision basis to effectively delay transvenous pacing and to protect venous access to the heart for further decades of cardiac pacing. To decrease the risk associated with mechanical lead damage, the use of bipolar Medtronic 4968 leads along with the activation of appropriate automatic polarity switch algorithms in the event of a detected change in impedance should be advocated. Further safety features might be considered in pacemaker-dependent patients, such as the placement of two ventricular pacing leads connected to a dual-chamber pulse generator for baseline and back-up VVI pacing through the atrial and ventricular port, respectively.[18] To increase battery longevity, generators with the AutoCapture™ feature and, of course, steroid-eluting leads should be preferred. Based on our current knowledge,[14,19] ventricular leads should preferentially be placed on the apex of the systemic ventricle to ensure optimal preservation of systemic ventricular synchrony and function. Such placement is possible from the subxiphoid approach in infants and smaller children, and carries a very acceptable cosmetic result. As no study so far has shown any advantage of dual-chamber vs. single-chamber ventricular pacing in small children with AV block and preserved cardiac function,[20–22] single-chamber pacing may be used unless otherwise indicated to limit the extent of the surgical approach.

Ethics

The study complies with the Declaration of Helsinki. Owing to the purely retrospective study design, using available institutional clinical records, with an absence of impact on management of the patients included and completely anonymous data presentation, informed consent of the subjects (or their parents) and ethical approval have not been obtained.

Conflict of interest: none declared.

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2. Differential effects of the site of permanent epicardial pacing on left ventricular synchrony and function in the young: implications for lead placement.

Souhrn

Cílem práce bylo porovnat vliv stimulace pravé (PK) a levé (LK) komory na synchronii kontrakce a systolickou funkci systémové LK. Do studie bylo zahrnuto 32 dětí s úplnou vrozenou (n = 15) nebo chirurgickou (n = 17) atrioventrikulární blokádou. Ejekční frakce LK a frakční zkrácení LK byly významně nižší ve skupině pacientů stimulovaných z volné stěny PK v porovnání s pacienty stimulovanými z hrotu LK nebo PK. Hodnoty parametrů dyssynchronie (interventricular mechanical delay [IVMD], septal to posterior wall motion delay [SPWMD], septal to lateral mechanical delay [SLMD]) byly naopak významně nižší u skupiny stimulovaných z hrotu LK v porovnání se skupinou stimulovaných z volné stěny PK. Ejekční frakce LK negativně korelovala se SPWMD (R^2 = 0,454, P < 0,001) a SLMD (R^2 = 0,320, P < 0,001). Stimulace z volné stěny PK (P = 0,014) a SPWMD (P = 0,044) byly v multivariátní analýze negativními prediktory ejekční frakce LK.

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CLINICAL RESEARCH

Differential effects of the site of permanent epicardial pacing on left ventricular synchrony and function in the young: implications for lead placement

Roman A. Gebauer[1]*, Viktor Tomek[2], Petr Kubuš[2], Vít Rázek[1], Tomáš Matějka[2], Aida Salameh[1], Martin Kostelka[3], and Jan Janoušek[1]

[1]Department of Pediatric Cardiology, Heart Center, University of Leipzig, Strümpellstrasse 39, 04289 Leipzig, Germany; [2]Kardiocentrum and Cardiovascular Research Center, University Hospital Motol, Prague, Czech Republic; and [3]Department of Cardiac Surgery, Heart Center, University of Leipzig, Leipzig, Germany

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Aims To analyse left ventricular (LV) synchrony and function with respect to the epicardial pacing site in the young.

Methods and results Left ventricular function and synchrony (M-mode, speckle tracking) were evaluated during mid-term follow-up in 32 children with complete non-surgical ($n = 15$) or surgical ($n = 17$) atrioventricular block (structural heart disease in 21/32) paced from LV apex ($n = 19$), right ventricular (RV) apex ($n = 7$), and RV free wall ($n = 6$), respectively. Data are in the following order: LV apical, RV apical, and RV free wall pacing. Septal to posterior wall motion delay (SPWMD) = median 0, 69, and 136 ms ($P < 0.001$), septal to lateral mechanical delay = 54 ± 29, 73 ± 24, and 129 ± 70 ms ($P = 0.001$), apical to basal mechanical delay = 96 ± 37, 106 ± 50, and 79 ± 18 ms (*P* NS), and LV ejection fraction (LVEF) = 57 ± 9, 49 ± 12, and 33 ± 10% ($P < 0.001$), respectively. Left ventricular ejection fraction correlated negatively with SPWMD ($R^2 = 0.454$, $P < 0.001$) and septal to lateral mechanical delay ($R^2 = 0.320$, $P < 0.001$) but not with apical to basal mechanical delay. Right ventricular free wall pacing ($P = 0.014$) and SPWMD ($P = 0.044$) were negative multivariable predictors of LVEF.

Conclusion Compared with other sites, LV apical pacing preserves septal to lateral LV synchrony and systolic function and may be the preferred epicardial pacing site in the young.

Keywords Permanent pacing • Heart block • Ventricular dysfunction • Left ventricular pacing • Right ventricular pacing • Children

Introduction

Right ventricular (RV) pacing is associated with asynchronous left ventricular (LV) activation,[1] which can lead to deleterious pathological remodelling and LV failure. Several recent studies have demonstrated that increased percentage of RV apical pacing correlates with morbidity and mortality from heart failure in adults.[2–4] Far less data are, however, available in children. Karpawich *et al.* described histological changes (myofibrillar hypertrophy, fibrosis, and fatty deposits) and depressed LV function in paediatric patients with congenital complete atrioventricular (AV) block and right ventricular apical pacing.[5] Recent paediatric studies have reported a 6.0–13.4% incidence of LV dysfunction in right ventricular paced children.[6–8] In young children, epicardial leads are preferred to transvenous placement because of the risk of venous thrombosis and technical implantation issues. Pacing from the epicardial RV free wall was, however, identified as a major risk factor for the development of pacing-associated LV dysfunction.[8] Alternative pacing sites have been looked for. Favourable acute haemodynamics and preserved LV synchrony were shown in both an experimental and a human study comparing LV apical pacing with other pacing sites or spontaneous ventricular activation.[9,10] Promising

* Corresponding author. Tel: +49 341 865 1036, Fax: +49 341 865 1143, Email: roman.gebauer@med.uni-leipzig.de

mid-term effects of epicardial LV free wall pacing when compared with RV pacing were reported in two recent studies.[11,12] Mid-term impact of paediatric LV apical pacing remains, however, undefined. The purpose of this study was to evaluate mid-term effects of LV apical pacing on LV synchrony and function when compared with RV epicardial-paced controls.

Methods

Patients

Left ventricular and RV epicardially paced patients were recruited from two tertiary care paediatric cardiac surgery centres. The indication for pacing was either a non-surgical or a surgical complete AV block. All patients had normal ventricular situs and a systemic LV and had either normal cardiac morphology or underwent successful correction of structural congenital heart disease. One hundred per cent ventricular pacing was required for inclusion into the study to ensure complete paced ventricular capture. The LV-paced group consisted of 19 consecutive patients who were provided with an epicardial LV apical lead since the introduction of this technique. The RV-paced group consisted of consecutive patients paced epicardially from either the RV free wall ($n = 7$) or RV apex ($n = 6$) coming to regular pacemaker follow-up over a period of 1 year. Their age at implantation and diagnosis matched the LV-paced cohort. Demographic data according to the pacing site are summarized in *Table 1*. There were no significant differences between the pacing sites except for the duration of pacing, which was significantly shorter in the LV-paced cohort.

Pacing

Pacing lead positions were assigned according to implantation protocol data and confirmed by chest X-rays in antero-posterior and lateral views and by QRS morphology. In case of a bipolar lead, the position of the stimulating electrode (cathode) was noted. Right bundle branch block morphology of the paced QRS complex along with superior axis was consistent with an LV apical lead placement. Left bundle branch block pattern along with superior axis was consistent with RV apical position and left bundle branch block along with leftward or inferior axis with RV free wall position, respectively.

Echocardiographic follow-up

Echocardiographic evaluation was performed by two different operators according to a uniform protocol using the Vivid 7 echocardiograhic machines (GE-Vingmed, Horten, Norway) without any specific effort to visualize the epicardial pacing lead position. Informed consent has been obtained from the patients or their guardians prior to the study. Digitally stored raw data were analysed off-line on the EchoPac workstation. The observers (R.A.G., V.T., not identical with the operators obtaining the echocardiographic data set) were blinded to the pacing site. Parasternal M-mode images were used to measure the LV end-diastolic and end-systolic dimensions. Measurements were taken at the point of peak diastolic LV free wall outward motion and peak systolic inward motion, respectively, and compared with the normal values of body weight-matched individuals[13] using the *z*-score method. Left ventricular fractional shortening (FS) was calculated according to the following formula: (LV end-diastolic dimension − LV end-systolic dimension)/LV end-diastolic dimension × 100. Left ventricular end-diastolic (LVEDV) and end-systolic volume (LVESV) were measured using the Simpson's biplane method and indexed to body surface area and ejection fraction (EF) was calculated. Colour Doppler echocardiography was performed for quantification of mitral regurgitation using usual semi-quantitative grading as none = 0, mild = 1, moderate = 2, and severe = 3.[14] Pulse wave Doppler from the LV and RV outflow tract was used to visualize the onset of ventricular ejection. The speckle-tracking method was applied to evaluate longitudinal two-dimensional (2D) strain in the apical four-chamber and long-axis views in four apical, four mid-ventricular, and four basal LV segments according to standardized myocardial segmentation.[15] To assess peak segmental systolic deformation timing, the time from QRS onset to peak systolic strain was measured in each segment.[16] Analysis was checked for reproducibility by comparing 2D strain measurements from two consecutive

Table 1 Demographics

Parameter	LV apical pacing ($n = 19$)	RV apical pacing ($n = 7$)	RV free wall pacing ($n = 6$)	*P*-value overall
Surgical AV block, *n*	11	3	3	0.781
Age at implantation (months), median (25/75% quartiles)	5.5 (0.6/35.6)	6.0 (1.0/15.0)	0.8 (0.3/2.8)	0.686
Duration of pacing (months), median (25/75% quartiles)	22.8 (13.0/35.5)	57.4 (32.7/113.1)	66.3 (39.0/94.5)	0.004
DDD(R) mode, *n*	13	2	4	0.171
Structural heart disease, *n*	12	4	5	0.574
Cardiac surgery, *n*	12	3	5	0.322
VSD/patch, *n*	4	2	2	
AVSD/correction, *n*	4	0	1	
ToF/correction, *n*	3	0	0	
d-TGA/switch, *n*	0	1	1	
CCTGA, VSD/double switch, *n*	1	0	0	
TV endocarditis, *n*	0	0	1	
ASD/Amplatzer occluder, *n*	0	1	0	

ASD, atrial septal defect; AV, atrioventricular; AVSD, atrioventricular septal defect; CCTGA, congenitally corrected transposition of the great arteries; LV, left ventricle/left ventricular; RV, right ventricle/right ventricular; d-TGA, d-transposition of the great arteries; ToF, Tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

cardiac cycles by the same observer (intra-observer variability) and measurements from one cycle by two different observers (inter-observer variability).

The following dyssynchrony indices were evaluated:[17]

(i) Inter-ventricular mechanical delay measured as the time difference between the LV and RV pre-ejection times.
(ii) Septal to posterior wall motion delay (SPWMD) measured as the time shift between peak systolic septal and LV posterior wall motion and/or thickening.[18]
(iii) Septal to lateral mechanical delay was calculated as the time shift between the earliest peak segmental systolic 2D strain in either the inferoseptal or anteroseptal basal or mid-ventricular segment and latest peak segmental systolic 2D strain in either the anterolateral or inferolateral basal or mid-ventricular segment.
(iv) Apical to basal mechanical delay was calculated as the time shift between the earliest apical and the latest basal peak segmental systolic 2D strain.
(v) Maximum LV mechanical delay was calculated as the difference between the earliest and latest peak systolic 2D strain in any of the evaluated 12 LV segments.
(vi) Standard deviation (SD) of the time to peak segmental systolic 2D strain in 12 LV segments.

Statistical analysis

Data are presented as mean (SD) or as median (25/75% quartiles). Multiple comparisons between different patient groups were performed by one-way analysis of variance followed by pair-wise multiple comparisons using the Holm–Sidak method for normally distributed data or by the Kruskal–Wallis one-way analysis of variance on ranks followed by pair-wise multiple comparisons by the Dunn's method in case of the absence of normal distribution. For comparisons of categorical variables, the χ^2 test was applied. Correlation between two variables was evaluated by linear regression. Backward stepwise regression was used to assess the effect of multiple independent variables on LVEF. Intra- and inter-observer variability of 2D strain measurements was tested by the coefficient of variation.[19] SigmaPlot for Windows Version 9.0 was used for all statistical workup. Significance level was accepted at $P < 0.05$.

Results

Left ventricular size and function

Right ventricular free wall-paced patients had significantly worse systolic LV function than those paced from the LV apex (lower LV FS, LVEF, and higher LVESVi) and RV apex (lower LV FS and LVEF) (*Table 2*). There was a weak negative correlation between LVEF and duration of pacing ($R^2 = 0.294$, $P = 0.001$, *Figure 1*). There was, however, no correlation of LVEF with pacing duration if only LV apical-paced individuals were analysed ($R^2 = 0.181$, $P = 0.069$).

Left ventricular synchrony

Acceptable intra-observer and inter-observer variability was achieved for time to peak systolic segmental 2D strain measurements (coefficient of variation = 5.55 and 2.40%, respectively). The dyssynchrony indices reflecting either the inter-ventricular synchrony (inter-ventricular mechanical delay) or septal to lateral LV synchrony (SPWMD and septal to lateral mechanical delay) were all significantly lower in the LV apical-paced group when compared with the RV free wall-paced patients (*Table 2*). The degree of global LV dyssynchrony reflected by maximum LV

Table 2 Left ventricular function and synchrony

	LV apical pacing[1] ($n = 19$)	RV apical pacing[2] ($n = 7$)	RV free wall pacing[3] ($n = 6$)	*P*-value			
				Overall	1 vs. 2	2 vs. 3	1 vs. 3
LVEDD (z-score), mean (SD)	0.6 (1.7)	0.4 (1.7)	0.4 (1.2)	0.904	–	–	–
LV FS (%), mean (SD)	41 (7)	32 (7)	18 (11)	<0.001	0.05	0.05	0.05
LVEDVi (mL/m^2 BSA), median (25/75% quartiles)	54 (42/62)	62 (54/63)	58 (50/74)	0.550	–	–	–
LVESVi (mL/m^2 BSA), mean (SD)	23 (8)	31 (9)	45 (19)	<0.001	NS	NS	0.05
LVEF (%), mean (SD)	57 (9)	49 (12)	33 (10)	<0.001	NS	0.05	0.05
QRS duration (ms), mean (SD)	130 (17)	151 (11)	165 (28)	<0.001	0.05	NS	0.05
IVMD (ms), mean (SD)	1 (23)	50 (14)	51 (28)	<0.001	0.05	NS	0.05
SPWMD (ms), median (25/75% quartiles)	0 (0/8)	69 (13/75)	136 (65/330)	<0.001	NS	NS	0.05
Septal to lateral mechanical delay (ms), mean (SD)	54 (29)	73 (24)	129 (70)	0.001	NS	0.05	0.05
Apical to basal mechanical delay (ms), mean (SD)	96 (37)	106 (50)	79 (18)	0.514	–	–	–
Maximum LV mechanical delay (ms), mean (SD)	98 (34)	113 (43)	141 (53)	0.088	–	–	–
Standard deviation of time to peak systolic segmental 2D strain (ms), mean (SD)	36 (14)	39 (12)	47 (14)	0.223	–	–	–

EF, ejection fraction; IVMD, inter-ventricular mechanical delay; LV, left ventricle/left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; RV, right ventricle/right ventricular; SD, standard deviation; FS, fractional shortening; SPWMD, septal to posterior wall motion delay; 2D, two-dimensional.

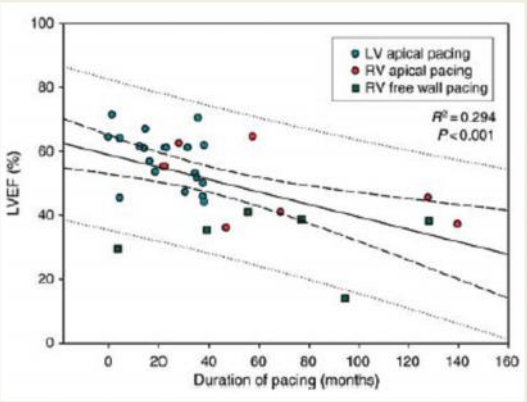

Figure 1 Correlation of LVEF and duration of pacing. Pacing sites are identified by respective symbols. Dotted lines, 95% prediction intervals; dashed lines, 95% confidence intervals.

mechanical delay and the SD of time to peak systolic segmental strain and the extent of apical to basal LV dyssynchrony did not, however, differ between pacing sites. Typical LV mechanical activation patterns for an RV free wall- and LV apical-paced individual are depicted in *Figure 2*.

Correlation between QRS duration and left ventricular synchrony

QRS duration was shorter in the LV apical-paced patients when compared with both the RV free wall- and RV apex-paced groups (*Table 2*). There were marginal correlations of SPWMD ($R^2 = 0.269$, $P = 0.002$) and maximum LV mechanical delay ($R^2 = 0.125$, $P = 0.047$) with QRS duration. None of the remaining dyssynchrony parameters showed any correlation with QRS length.

Correlation between left ventricular function and synchrony

Left ventricular ejection fraction was significantly inversely correlated with SPWMD ($R^2 = 0.454$, $P < 0.001$), maximum LV mechanical delay ($R^2 = 0.329$, $P < 0.001$), septal to lateral mechanical delay ($R^2 = 0.320$, $P < 0.001$, *Figure 3*), inter-ventricular mechanical delay ($R^2 = 0.298$, $P = 0.001$), and SD of the time to peak segmental systolic 2D strain ($R^2 = 0.252$, $P = 0.003$) but not with the apical to basal mechanical delay ($R^2 = 0.038$, *P* NS; *Figure 3*). Multivariable analysis identified the RV free wall pacing ($P = 0.014$) and SPWMD ($P = 0.044$) but not the age at first pacemaker implantation, duration of pacing, pacing mode, AV block aetiology, the presence of structural heart disease, or history of cardiac surgery (*P* NS for all) as significant negative predictors of LVEF.

Procedure complications and clinical outcome

There were no pacemaker implantation-related complications in either the RV- or the LV-paced patients. All but one patient in the RV free wall-paced group tolerated LV dysfunction well either without treatment or on anticongestive medication (three of six patients). One patient from this group after correction of complete AV septal defect and subsequent mitral valve replacement had to be upgraded to biventricular pacing because of progressive LV failure. His LVEF improved afterwards from 30 to 46%.

Discussion

Severe LV dysfunction is occasionally found in paediatric patients with permanent ventricular pacing[6,7] and resolves successfully after cardiac resynchronization.[20,21] A recently published population-based study suggested that epicardial RV free wall pacing may be a major risk factor for the development of pacing-associated LV failure.[8] Left ventricular free wall-based pacing[11,12] or reposition of the pacing lead from the RV to the LV[22] has been shown to preserve and improve LV function, respectively. Acute haemodynamic studies both in experiment and in children have further indicated that LV apical pacing (when compared with RV or LV free wall pacing) may carry least dyssynchrony and haemodynamic derangement.[9,10]

This study sought to compare three different permanent epicardial pacing sites in terms of LV synchrony and function. There were four major findings: (i) systolic LV dysfunction correlated significantly with dyssynchrony indices reflecting septal to lateral mechanical delay, (ii) LV apical pacing resulted in significantly less septal to LV free wall dyssynchrony thus keeping segments most important for global LV function (basal and mid-ventricular) synchronous, (iii) LV function was better preserved with pacing from the LV apex, and (iv) RV free wall pacing was most detrimental to both LV synchrony and function (a finding consistent with recently published retrospective data).[8] Interestingly, there were no differences in apical to basal dyssynchrony or global LV dyssynchrony between the three pacing sites. Also, there was either no or only a marginal correlation between dyssynchrony indices and QRS duration, indicating a disparity between electrical and mechanical dyssynchrony.

Such findings have important implications for ventricular lead placement in the paediatric age group: (i) choice of the pacing site should be dictated by haemodynamic aspects and not by surgeon's preference, and (ii) in view of preservation of LV synchrony and function in this and other recent studies LV-based pacing should be the preferred option in cases of epicardial lead placement in patients with a systemic LV. It remains to be seen whether the specific choice of the LV pacing site will make any difference in the long term.

This study has several limitations: (i) clear differences between RV apical pacing and the remaining two pacing sites could not be elaborated because of the size of the samples. It seems, however, that in terms of LV dyssynchrony and function, RV apical-paced patients do behave worse than those paced from the LV apex but better than patients paced from the RV free wall; (ii) RV-paced individuals had longer pacing duration and this may have itself adversely influenced their systolic LV function. However, no dependence of LVEF on duration of pacing could be found in the LV apical-paced group and multivariable analysis did not show a significant influence of the pacing duration on LVEF; (iii) 20 of the 32 study patients underwent heart surgery

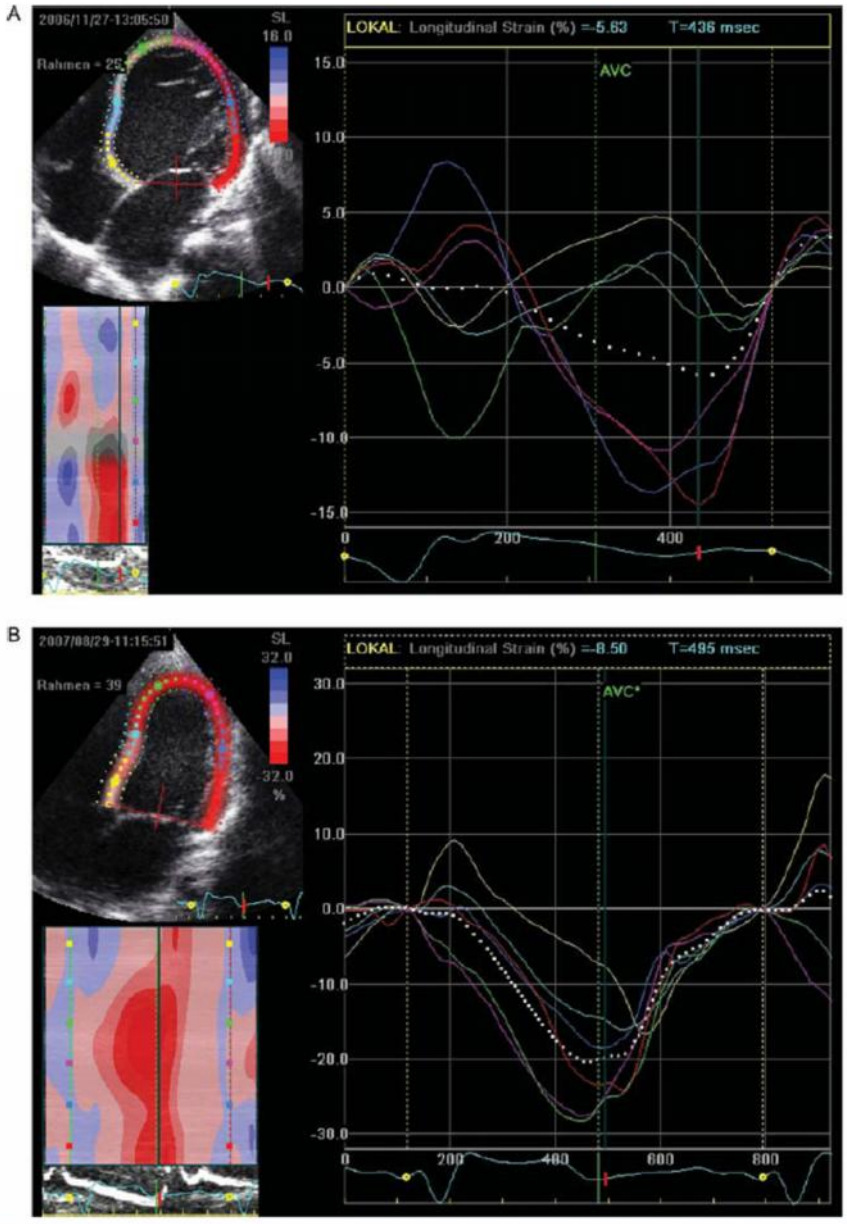

Figure 2 (*A*) Typical mechanical activation pattern in RV free wall pacing showing early peak negative 2D strain in the basal and mid-ventricular septum (coded yellow and light blue) and late negative strain peak in the LV free wall (red and dark blue). An extensive septal to lateral mechanical delay of 300 ms is evident. (*B*) Left ventricular apical pacing with mechanical activation starting at the apex (green and violet coded) and proceeding to the LV base (red and yellow coded). Septal to lateral mechanical delay is only −80 ms in this case with an earlier free wall than septal contraction. Note the difference in time scale between (*A*) and (*B*).

having potential influence on LV function. There was, however, a similar distribution of structural heart disease and cardiac surgery between pacing sites and these variables were not predictive of LV function in a multivariable analysis; and (iv) LV apical pacing carried a similar extent of apical to basal dyssynchrony as RV pacing, which may lead to LV dysfunction over a longer time period. This cannot be excluded by the current data. Basal and mid-ventricular segments are, however, the greatest contributors to global LV function and dyssynchrony at this level (septal to lateral) should have more pronounced long-term impact.

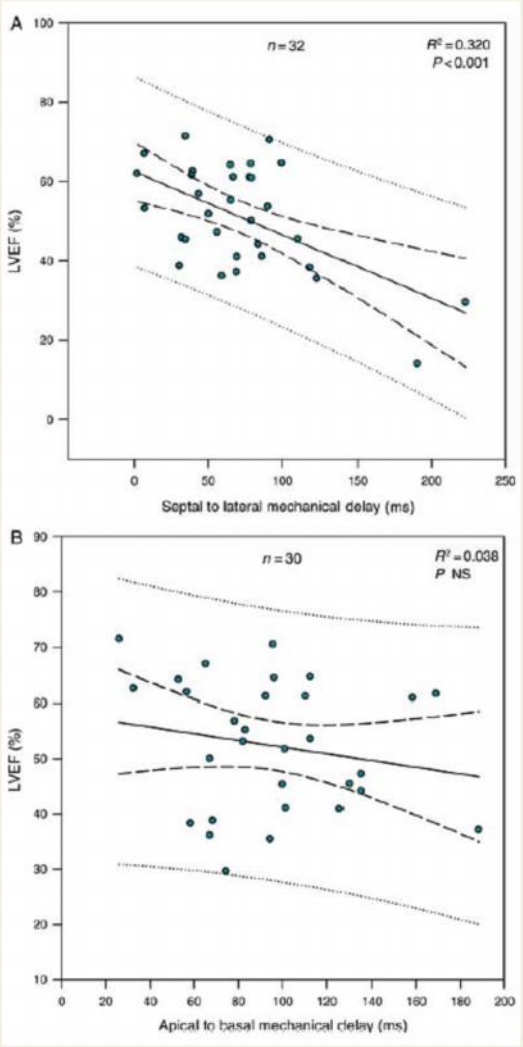

Figure 3 (*A*) Negative correlation of LVEF with septal to lateral mechanical delay. (*B*) The absence of correlation with the apical to basal mechanical delay. LVEF, left ventricular ejection fraction. Dotted lines, 95% prediction intervals; dashed lines, 95% confidence intervals.

Conclusion

Left ventricular apical stimulation is a promising alternative, minimizing septal to lateral LV dyssynchrony and preserving LV function and may be preferred in young patients with a systemic LV requiring permanent epicardial pacing.

Conflict of interest: none declared.

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3. Impact of the permanent ventricular pacing site on left ventricular function in children: a retrospective multicentre survey.

Souhrn

Do multicentrické retrospektivní observační studie bylo zahrnuto 297 pacientů ve věku <18 let se strukturálně normálním srdcem a trvalou kardiostimulací pro atrioventrikulární blokádu. Vstupním kritériem byla převažující komorová stimulace (> 70 % stimulovaných stahů) a trvání stimulace > 1 rok. Pacienti byli rozděleni do skupin dle místa stimulace – pravá komora (PK) epikardiálně (RVepi, n = 147), PK endokardiálně (RVendo, n = 113) a levá komora (LK) epikardiálně (LVepi, n = 37). Pro hodnocení jednotlivých parametrů byla použita echokardiografická vyšetření při poslední ambulantní kontrole. Frakční zkrácení LK ve skupině LVepi (39 ± 5 %) bylo významně vyšší než ve skupinách RVendo (33 ± 7 %, P < 0,001) a RVepi (35 ± 8 %, P = 0,001), bez významného rozdílu mezi RVendo a RVepi (P = 0,275). Subnormální ejekční frakce LK (< 50 %) byla přítomna u 17/69 (25 %) pacientů ve skupině RVendo a 10/35 (29 %) ve skupině RVepi. Ejekční frakce LK ≥ 50 % byla u 17/18 (94 %) pacientů ve skupině LVepi. Místo trvalé kardiostimulace je tedy u dětí s izolovanou AV blokádou významným faktorem pro zachování funkce LK.

Impact of the permanent ventricular pacing site on left ventricular function in children: a retrospective multicentre survey

Irene E van Geldorp,[1,2] Tammo Delhaas,[2,3] Roman A Gebauer,[4] Patrick Frias,[5] Maren Tomaske,[6] Mark K Friedberg,[7] Svjetlana Tisma-Dupanovic,[8] Jan Elders,[9] Andreas Früh,[10] Fulvio Gabbarini,[11] Petr Kubuš,[12] Viera Illikova,[13] Sabrina Tsao,[14] Andreas Christian Blank,[15] Anita Hiippala,[16] Thierry Sluysmans,[17] Peter Karpawich,[18] Sally-Ann Clur,[19] Xavier Ganame,[20] Kathryn K Collins,[21] Gisela Dann,[22] Jean-Benoît Thambo,[23] Conceição Trigo,[24] Bert Nagel,[25] John Papagiannis,[26] Annette Rackowitz,[27] Jan Marek,[28] Jan-Hendrik Nürnberg,[29] Ward Y Vanagt,[2,20,30] Frits W Prinzen,[30] Jan Janousek,[12] for the Working Group for Cardiac Dysrhythmias and Electrophysiology of the Association for European Paediatric Cardiology*

*For numbered affiliations see end of article.

Correspondence to
Irene E van Geldorp, Cardiovascular Research Institute Maastricht, Department of Cardiology, Maastricht University Medical Center, PO Box 616, Maastricht NL-6200 MD, The Netherlands; i.vangeldorp@maastrichtuniversity.nl

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ABSTRACT

Background Chronic right ventricular (RV) pacing is associated with deleterious effects on cardiac function.

Objective In an observational multicentre study in children with isolated atrioventricular (AV) block receiving chronic ventricular pacing, the importance of the ventricular pacing site on left ventricular (LV) function was investigated.

Methods Demographics, maternal autoantibody status and echocardiographic measurements on LV end-diastolic and end-systolic dimensions and volumes at age <18 years were retrospectively collected from patients undergoing chronic ventricular pacing (>1 year) for isolated AV block. LV fractional shortening (LVFS) and, if possible LV ejection fraction (LVEF) were calculated. Linear regression analyses were adjusted for patient characteristics.

Results From 27 centres, 297 children were included, in whom pacing was applied at the RV epicardium (RVepi, n=147), RV endocardium (RVendo, n=113) or LV epicardium (LVepi, n=37). LVFS was significantly affected by pacing site (p=0.001), and not by maternal autoantibody status (p=0.266). LVFS in LVepi (39±5%) was significantly higher than in RVendo (33±7%, p<0.001) and RVepi (35±8%, p=0.001; no significant difference between RV-paced groups, p=0.275). Subnormal LVFS (LVFS<28%) was seen in 16/113 (14%) RVendo-paced and 21/147 (14%) RVepi-paced children, while LVFS was normal (LVFS≥28%) in all LVepi-paced children (p=0.049). These results are supported by the findings for LVEF (n=122): LVEF was <50% in 17/69 (25%) RVendo- and in 10/35 (29%) RVepi-paced patients, while LVEF was ≥50% in 17/18 (94%) LVepi-paced patients.

Conclusion In children with isolated AV block, permanent ventricular pacing site is an important determinant of LV function, with LVFS being significantly higher with LV pacing than with RV pacing.

INTRODUCTION

In patients with bradycardia due to complete atrioventricular (AV) block, ventricular pacing is required to normalise heart rate. The pacing-induced activation pattern is characterised by a prolonged total activation duration and an abnormal sequence of activation (in both longitudinal and transverse directions). This abnormal electrical activation pattern may lead to dyssynchronous ventricular contraction, the degree of dyssynchrony varying with the site of pacing.[1] Ventricular pacemaker electrodes are conventionally positioned either at the right ventricular (RV) endocardium or at the RV epicardium. However, RV pacing results in a left bundle branch block morphology and is associated with cardiac dysfunction and remodelling.[2–7] The preservation of cardiac function during chronic ventricular pacing should be a high priority, especially in paediatric patients who are usually paced from an early age and may expect lifelong pacing. The main objective of this multicentre study was to investigate whether left ventricular (LV) pacing sites, in comparison with RV endocardial and RV epicardial pacing sites, have fewer adverse long-term functional and structural effects, and may prevent pacing-induced LV dysfunction in children with isolated AV block.

MATERIALS AND METHODS

Study population

From the institutional databases of the participating 27 centres, patients with a structurally normal heart and isolated advanced second-degree or complete AV block with chronic and permanent ventricular pacing for rate control (minimum of 1 year follow-up, minimum of 70% ventricular paced beats) were identified. All these patients were considered for inclusion. Exclusion criteria were postsurgical AV block, structural congenital heart disease and evident cardiomyopathy due to causes other than AV block. Study end points were reached whenever patients reached 18 years of age, underwent a change in pacing site, received cardiac resynchronisation therapy or cardiac transplantation for heart failure, or died. For

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those cases, data from the last echocardiography before the event were used.

Data

Demographic data and clinical characteristics (gender, age, body surface area, aetiology of AV block, maternal autoantibody status, year of pacemaker implantation, duration of pacing) were collected. Parameters from the last echocardiography performed at a routine follow-up visit at age <18 years were reviewed. In all patients, LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were assessed. The degree of LV dilatation was evaluated by adjusting LVEDD for body size, expressed as a *z*-score.[8] As a measure of LV function, LV fractional shortening (LVFS) was calculated (LVFS=(LVEDD−LVESD)/LVEDD×100%). According to generally accepted criteria,[8 9] we classified LVFS as 'normal' (LVFS ≥28%), 'subnormal' (LVFS <28%) or 'depressed' (LVFS <25%). For the subset of patients in whom end-diastolic and end-systolic LV volumes (LVEDV and LVESV, respectively) were assessed, LV ejection fraction (LVEF) was calculated (LVEF=(LVEDV−LVESV)/LVEDV*100%). Mitral regurgitation was scored on a scale from 0 (= no regurgitation) to 4 (= severe regurgitation).

Based on the location of the tip of the ventricular pacing electrode (the site of pacing), the cohort was divided into three groups: RV epicardium (RVepi), RV endocardium (RVendo), or LV epicardium (LVepi).

Statistical analysis

Comparisons between groups were performed with analysis of variance or χ^2 tests, as appropriate. Linear regression analyses were used to examine whether LVFS and LVEDD *z*-scores differed between the groups (ie, between pacing sites). These analyses were adjusted for the following covariates: maternal autoantibody status ('positive', 'negative', or 'unknown'), year of pacemaker implantation, age at implantation, participating centre and duration of pacing and body surface area at echocardiographic follow-up. The influence of pacing mode (VVI vs DDD) on LVFS was investigated only in the subset of patients for whom pacing mode at follow-up was reported.

Additionally, to carefully investigate the potential influence of maternal autoantibody status on LV function, linear regression analyses were performed on the study population grouped into 'autoantibody positive', 'autoantibody negative' and 'unknown autoantibody status'. In these analyses, 'pacing site' was included as a covariate in addition to above-mentioned characteristics.

Group characteristics are expressed either as mean±SD, or as proportion (%). Mean differences in LVFS and LVEDD adjusted for covariates are expressed as effect sizes (β) with 95% CIs, $p<0.05$ = significant.

RESULTS

Study population: demographic data and clinical characteristics

A total of 297 children, from the institutional databases of the 27 participating centres, were included in the study. Pacing site distribution was: RVendo (n=113), RVepi (n=147), and LVepi (n=37). Maternal autoantibody status (anti-SSA (Ro), anti-SSB (La)) was reported for 201 (68%) of the patients. Maternal autoantibodies were present in 88 (44%) of these. Patient characteristics summarised for each pacing site are listed in table 1. With the above-mentioned numbers of patients in each group, it would be possible to detect differences in LVFS between the pacing site groups with a power >90% (μ=5% points; SD 8% points; α=0.05; unequal groups).

Table 1 Patient characteristics

Characteristics	RV endo (n=113)	RV epi (n=147)	LV epi (n=37)	p Value
Gender (M/F; %)	50/50	44/56	46/54	0.692
Aetiology of AV block				
Congenital/infectious/unknown (%)	69/3/28	85/1/14	92/0/8	0.126
Anti-Ro/La antibodies: +/−/unknown (%)	17/38/45	40/43/17	27/19/54	<0.001
Age at implantation (years)	7.9±4.1	2.0±2.4	2.7±3.5	<0.001*
Age at follow-up (years)	13.8±3.4	7.4±4.2	7.3±4.5	<0.001*
BSA at follow-up (m^2)	1.5±0.3	0.9±0.3	0.9±0.4	<0.001*
Duration of pacing at follow-up (years)	5.9±3.4	5.4±3.6	4.6±3.1	0.108
Year of implantation, (expressed as years since implantation until July 2010)	8.9±4.0	8.2±4.5	8.1±6.1	0.468
QRS duration (paced; ms)	146±19	139±20	148±24	0.004†
Pacing mode at follow-up				
VVI/DDD/not reported (%)	32/50/18	46/40/14	22/38/40	0.059

*No significant differences between RVepi and LVepi (p=0.229, p=0.809 and p=0.837 for age at implantation, age at follow-up and BSA at follow-up, respectively).
†RVepi versus RVendo, p=0.005; RVepi versus LVepi, p=0.012; RVendo versus LVepi, p=0.545.
AV block, atrioventricular block; BSA, body surface area; LVepi, left ventricular epicardial pacing; RVendo, right ventricular endocardial pacing; RVepi, right ventricular epicardial pacing.

Effect of pacing site on left ventricular fractional shortening and dilatation score

At routine follow-up, LVFS was significantly higher in children with LVepi pacing (39±5%) than in children with RVendo pacing (33±7%) and RVepi pacing (35±8%) (figure 1). Pacing site was the solitary significant determinant (p=0.001) of LVFS (maternal autoantibody status, p=0.266; duration of pacing, p=0.833; body surface area at follow-up, p=0.882; centre, p=0.560; year of implantation, p=0.182; and age at implantation, p=0.809). The mean LVFS differences adjusted for covariates (ie, 'effect size β') are reported in table 2.

In the subgroup of patients for whom the pacing mode (either VVI or DDD) at follow-up was reported (n=242), pacing mode

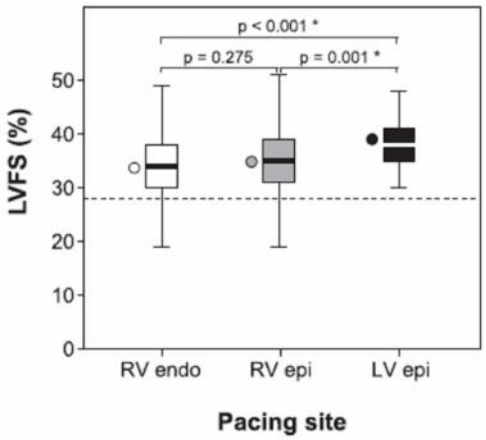

Figure 1 Left ventricular fractional shortening after chronic ventricular pacing. Left ventricular fractional shortening (LVFS), a measure of LV function, was significantly (*) higher in children being paced at the LV epicardium (LVepi) than in children being paced at the RV epicardium (RVepi) or RV endocardium (RVendo). Box plots represent 25th, 50th and 75th centiles. Whiskers represent the minimal and maximal values within the range of (25th centile − 1.5×IQR) and (75th centile + 1.5×IQR), respectively. Dots display mean values.

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Table 2 Mean differences in left ventricular fractional shortening and dilatation score

	Effect size β	95% CI	p-value
LVFS			
LVepi vs RVepi	+4.7%-points	1.9% to 7.5 %-points	0.001*
LVepi vs RVendo	+6.1%-points	2.9% to 9.3 %-points	<0.001*
RVepi vs RVendo	+1.4%-points	−1.1% to 3.9 %-points	0.275
LVEDD z-score			
LVepi vs RVepi	−0.1	−0.5 to 0.3	0.579
LVepi vs RVendo	−0.3	−0.8 to 0.2	0.268
RVepi vs RVendo	−0.2	−0.5 to 0.2	0.428

Effect size β=mean difference between groups, adjusted for covariates.
*Significant mean difference between the groups.
LVEDD, left ventricular end-diastolic diameter; LVepi, left ventricular epicardial pacing; LVFS, left ventricular fractional shortening; RVendo, right ventricular endocardial pacing; RVepi, right ventricular epicardial pacing.

was not a significant determinant (p=0.209) while pacing site remained a significant determinant of LV function (p=0.002). Differences between pacing sites, adjusted for pacing mode in addition to the other covariates, were similar to the effect sizes reported in table 2.

LVEDD *z*-score was normal in all groups (RVendo 0.0±1.3; RVepi 0.4±1.1; LVepi 0.3±0.9, figure 2), and was not significantly influenced by pacing site (p=0.640), or by maternal autoantibody status (p=0.724) or any of the other covariates. The adjusted means were not significantly different as presented in table 2.

Depressed LV function in ~10% of the chronically RV-paced patients

LVFS was subnormal (LVFS <28%) in 16 RVendo- (14%) and 21 RVepi-paced patients (14%). In more detail, LVFS was depressed (LVFS <25%) in 10 (9%) of the RVendo-paced and in 17 (12%) of the RVepi-paced patients. In contrast, LVFS was normal (LVFS ≥28%) in all patients in whom LV pacing was applied (p=0.049, χ^2 test).

In the subset of patients for whom we could calculate LVEF (n=122), LVEF was <50% in 17/69 (25%) RVendo-paced and in 10/35 (29%) RVepi-paced patients, whereas this was only the case in one of the 18 (6%) LVepi-paced patients.

Mitral regurgitation

Distribution of mitral regurgitation scores was significantly different between the pacing site groups (p=0.032, χ^2 test). Mitral regurgitation was mild (score 1) in 42 (29%) RVepi-paced and in 19 (17%) RVendo-paced patients, but only in three (8%) LVepi-paced patients. Score '2' was reported for four patients (RVepi n=1; RVendo n=2, LVepi n=1), while none of the patients had moderate to severe mitral regurgitation (scores 3 and 4).

Influence of maternal autoantibody status

As shown by the analyses grouped by pacing site, LVFS was significantly affected by pacing site (p=0.001), while maternal autoantibody status did not affect either LVFS, or LVEDD *z*-score (p=0.266 and p=0.724, respectively). These results were confirmed when analyses were performed on the same population grouped by maternal autoantibody status. For the three groups, mean LVFS and LVEDD *z*-scores were comparable: 34±8% and 0.4±1.3 for 'positive', 35±7% and 0.1±0.9 for 'negative' and 34±8% and 0.1±1.3 for 'unknown' maternal autoantibody status (LVFS and LVEDD *z*-score, respectively). Maternal autoantibody status was not a significant determinant of either LVFS (p=0.386) or LVEDD *z*-score (p=0.901), while pacing site remained a significant determinant of LVFS (p=0.013).

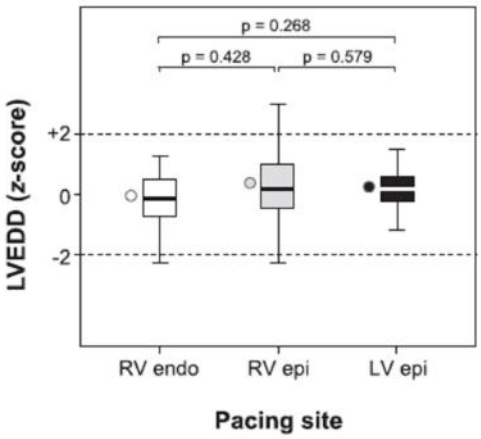

Figure 2 Left ventricular dilatation-score after chronic ventricular pacing. The *z*-score for left ventricular end-diastolic diameter (LVEDD *z*-score), a measure of LV dilatation, was not significantly influenced by the site of pacing. The LVEDD *z*-score was normal for all groups and differences between the pacing groups were not significant. Box plots represent 25th, 50th and 75th centiles. Whiskers represent the minimal and maximal values within the range of (25th centile − 1.5×IQR) and (75th centile + 1.5×IQR), respectively. Dots display mean values. LVepi, LV epicardium; RVendo, RV endocardium; RVepi, RV epicardium,

DISCUSSION

This multicentre study retrospectively surveys LV function and dimensions in 297 children with structurally normal hearts and chronic ventricular pacing for isolated AV block. In these patients, requiring lifelong chronic ventricular pacing, preservation of cardiac functional and structural integrity is a major challenge. This study indicates that pacing site significantly influences LVFS, with better LVFS in LVepi-paced patients than in RVepi-paced or RVendo-paced patients.

Pacing site influences left ventricular function

In this survey, LV function was found to be subnormal (LVFS <28%) in 14%, and depressed (LVFS <25%) in ~10% of the RVepi- and endo-paced patients. Our findings on LVFS are supported by those in the subset of patients for whom we were able to calculate LVEF: the proportion of patients with subnormal LVEF (LVEF <50%) was for each pacing group comparable to the proportion of patients with subnormal LVFS. Several other studies report that, within less than a decade of pacing, 7–10% of chronically RV-paced patients develop heart failure and that up to 13% have depressed LV function combined with LV dilatation.[2 10 11] Chronic RV pacing, rather than the aetiology of AV block, has been identified as an independent risk factor for development of LV dilatation and dysfunction.[11 12] This study indicates that it is predominantly the pacing site that affects LV function, as reflected by (1) a higher LVFS in the LV-paced group than in the RV-paced groups; (2) pacing site being the only significant factor influencing LVFS and (3) dissimilar incidence of patients with LVFS<28% between the pacing site groups. Moreover, maternal autoantibody status did not significantly influence LV function or LV dilatation score.

Though it appears that there are relevant proportions of patients who do not tolerate RV pacing, the reasons are not elucidated in this retrospective study. Chronic LV pacing, however, seems to be well tolerated by all patients, as suggested by absence of LV dysfunction in the LV-paced group. From the latter finding we hypothesise that pacing-induced LV

failure in children with structurally normal hearts might be prevented by LV pacing.

Potential reasons for preservation of LV function by LV pacing

We postulate that, above and beyond synchrony (reflected by the total duration of activation), the sequence of activation is a major determinant of cardiac pump function.[1 13] In LV pacing the pattern of activation and mechanical contraction pattern may be more favourable than patterns induced by RV pacing. During LV (free wall) pacing, the total duration of activation is prolonged similarly to that during RV free wall pacing, reflected by a similar QRS duration.[14] However, in contrast to RV pacing, LV pacing activates the LV lateral wall before the septum and RV lateral wall, preventing paradoxical septal movement and resulting in better haemodynamic performance than with RV pacing.[1 15] Furthermore, LV apical pacing induces physiological apex-to-base activation, which results in synchronous electrical activation and contraction around the circumference of the left ventricle.[16 17] These remarks are supported by the observation of Gebauer *et al*, that LV apical pacing preserves septal-to-lateral LV mechanical synchrony as well as systolic function.[18] Also, experimental studies have shown that LV apical pacing is better than pacing at other sites and that it maintains cardiac function at a normal level.[19 20]

Single-site left ventricular pacing versus biventricular pacing

Biventricular pacing is often used to resynchronise electrical activation in patients with either intrinsic or pacing-induced dyssynchrony and LV dysfunction. Biventricular pacing (following chronic RV pacing) improves pump function and reverses ventricular remodelling in children at least as effectively as in adults with heart failure.[21–23] Although single-site LV pacing and biventricular pacing have not yet been compared in children, single-site LV pacing in adults with heart failure results in the same improvement in LV function as acute or chronic biventricular pacing.[24–26] Also, animal experiments have indicated that single-site LV apical and LV septal pacing maintain cardiac function and efficiency at least as well as biventricular pacing.[19] The use of a single optimal ventricular pacing site provides advantages over biventricular pacing, such as lower pacemaker battery usage and a reduction in the number of surgical access routes required and consequent scar tissue formation.

Clinical implications of this study

Since paediatric patients with AV block are usually paced from an early age and require lifelong pacing, preservation of cardiac function during chronic ventricular pacing is important. This study indicates that LV pacing may be better than RV pacing if LV function is concerned. In the individual patient, depressed LV function (as seen in ~10% of the RV-paced patients) may indicate that chronic pacing is not well tolerated and that there may be a higher risk for pacing-induced heart failure. The median follow-up of pacing in this study, as in other studies, was less than a decade, which is a mere fraction of the lifelong follow-up expectancy of a child receiving ventricular pacing for complete AV block. The (very) long-term outcome of either RV or LV pacing beginning in childhood is still unknown. Considering the findings of this and other studies,[14 27 28] we suggest the use of a single LV apex or LV free wall site for chronic ventricular pacing in children with AV block and structurally normal hearts. Unfortunately, as each ventricle brings a continuum of possible pacing sites, and accuracy of (retrospective) determination of the precise site is limited, this survey has not provided exact data to reliably test which spot on the left ventricle would be the best, or whether certain sites within the right ventricle might be better than others.[7]

It is important not to simply extrapolate the results of this study to children with structural congenital heart disease. Nevertheless, results are likely to be applicable to patients with a systemic left ventricle, without intrinsic RV activation delay.

Practical considerations

Surgical access for LV pacing via a left lateral thoracotomy is minimal, easy and safe, though invasive.[29] In small children, the LV apex can easily be reached by a sub-xiphoidal approach, thereby avoiding a lateral thoracotomy, and with reasonable cosmetic results. Acknowledging the potential surgical complications, we particularly suggest implantation of electrodes at the LV epicardium if there are also other indications for a surgical approach.[30] In larger children, single-site epicardial LV pacing may also be achieved by a transvenous approach via the coronary sinus. In the near future, endocardial pacing in the systemic ventricle may become feasible through the application of 'wireless pacing'. However, in practice, the routine transvenous approach seems justifiable in young adults, as RV apical pacing is well tolerated by most patients.[10 31]

Regular follow-up with echocardiography to detect LV deterioration at an early stage is warranted in all paced patients receiving chronic ventricular pacing. Changing to either biventricular or single-site pacing at the systemic ventricle should be considered when echocardiography discloses signs of progressive ventricular dysfunction.[21 22 32–34]

Study limitations

The retrospective design of the study is a disadvantage, mainly because it hampers the use of sophisticated echocardiographic parameters. The shortening fraction is a limited marker for systolic function, and it may be affected by intraventricular asynchrony. Nevertheless, it was chosen as a main outcome parameter, as it is the most consistently measured variable in this population. Data on LVFS in the entire study population were supported by data on LVEF in those patients for whom LV volumes were available. The possibility of unintended bias for the effect of pacing from the various sites cannot totally be excluded since measurements were not performed blinded to the pacing site. However, at the time of the echocardiographic examination, there was no intention to compare the effects of different pacing sites. Each centre identified patients eligible for the study by systematically reviewing the institutional database. The structure of the database affected the time span of inclusion, and therefore also the number of patients from each centre. The number of LV-paced patients included in this study is relatively small in respect to the number of patients in the RV-paced groups, since LV pacing (for first implantation) is only used at a minority of centres. However, patients from several different centres are included for each pacing group (nine centres for the LV-paced group). Besides, 'participating centre' was entered as a covariate in the analysis to correct for potential bias arising from centre-based differences.

Future studies with larger numbers of LV-paced patients, more sophisticated echocardiographic indices and longitudinal follow-up are needed to confirm the conclusions of this survey, and to explore the effect of pacing site on parameters other than LV function.

CONCLUSION

In children with normal cardiac anatomy and AV block, the site of pacing is an important determinant of LV function, with

LVFS being significantly higher in children with chronic LV pacing than in children with chronic RV pacing. LVFS was subnormal (LVFS <28%) in 14% of the RV-paced children, whereas LVFS was normal in all LV-paced children.

Author affiliations
[1]Department of Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, The Netherlands
[2]Department of Pediatrics, Maastricht University Medical Center, Maastricht, The Netherlands
[3]Department of Biomedical Engineering, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands
[4]Department of Pediatric Cardiology, Heart Center, University of Leipzig, Leipzig, Germany
[5]Sibley Heart Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, USA
[6]Paediatric Cardiology, University Children's Hospital, Zürich, Switzerland
[7]Devision of Cardiology, Hospital for Sick Children, Toronto, Canada
[8]Department of Cardiology, Children's Mercy Hospital, Kansas City, USA
[9]Department of Pediatric Cardiology, Universitair Medisch Centrum St. Radboud, Nijmegen, The Netherlands
[10]Department of Pediatric Cardiology, Oslo University Hospital, Oslo, Norway
[11]Department of Pediatric Cardiology, Ospedale Infantile Regina Margherita, Turin, Italy
[12]Cardiocentrum and Cardiovascular Research Center, University Hospital Motol, Prague, Czech Republic
[13]Department of Pediatric Cardiology, Children's Cardiac Center, Bratislava, Slovakia
[14]Department of Electrophysiology, Children's Memorial Hospital, Chicago, USA
[15]Department of Pediatric Cardiology, Wilhelmina Kinderziekenhuis, University Medical Center, Utrecht, The Netherlands
[16]Department of Pediatric Cardiology, Hospital for Children and Adolescents, Helsinki University Hospital, Helsinki, Finland
[17]Department of Pediatric and Congenital Cardiology, Clinique Universitaire Saint-Luc, Brussels, Belgium
[18]Department of Cardiac Electrophysiology, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, USA
[19]Department of Pediatric Cardiology, Emma Kinderziekenhuis, Academisch Medisch Centrum, Amsterdam, The Netherlands
[20]Department of Pediatric Cardiology, University Hospital Gasthuisberg, Leuven, Belgium
[21]Department of Pediatric Cardiology, Children's Hospital University of Colorado, Denver, USA
[22]Department of Pediatric Cardiology, University Hospital Göttingen, Göttingen, Germany
[23]Department of Congenital Heart Disease, Hôpital Cardiologique du Haut-Lévêque, Bordeaux University, Bordeaux-Pessac, France
[24]Department of Pediatric Cardiology, Santa Marta Hospital, Lisbon, Portugal
[25]Department of Pediatric Cardiology, University Children's Hospital, Graz, Austria
[26]Department of Pediatric Cardiology, Mitera Children's Hospital, Maroussi, Greece
[27]Department of Pediatric Cardiology, Sophia Kinderziekenhuis, Erasmus University Medical Center, Rotterdam, The Netherlands
[28]Department of Cardiothoracics, Great Ormond Street Hospital, London, United Kingdom
[29]Department of Congenital Heart Disease and Pediatric Cardiology, Klinikum Links der Weser, Bremen, Germany
[30]Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands

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4. **Permanent cardiac pacing in children: choosing the optimal pacing site: a multicenter study.**

Souhrn

Retrospektivní a průřezová observační studie hodnotící vliv místa komorové stimulace na synchronii kontrakce a funkci levé komory (LK) u dětí (n = 178) se strukturálně normálním srdcem vyžadujících trvalou kardiostimulaci pro atrioventrikulární blokádu. Mechanická synchronie a funkce LK byly významně ovlivněny místem stimulace a byly významně vyšší u pacientů stimulovaných z hrotu LK/laterální stěny LK. Dyssynchronie LK inverzně korelovala s ejekční frakcí LK (R = 0,80, P = 0,031). Stimulace z výtokového traktu pravé komory/laterální stěny PK byla významným prediktorem snížené funkce LK (ejekční frakce LK < 45 %, OR = 10,72, 95% CI 2,07 – 55,60, P = 0,005), zatímco stimulace z hrotu LK/laterální stěny LK byla spojena se zachováním funkce LK (ejekční frakce LK ≥ 55 %, OR = 8,26, 95% CI 1,46 – 47,62, P = 0,018). Místo stimulace bylo jediným významným (P < 0,0001) prediktorem frakce zkrácení a ejekční frakce LK v multivariátní analýze.

Permanent Cardiac Pacing in Children: Choosing the Optimal Pacing Site

A Multicenter Study

Jan Janoušek, MD, PhD; Irene E. van Geldorp, MD; Sylvia Krupičková, MD, PhD; Eric Rosenthal, MD; Kelly Nugent, BSc; Maren Tomaske, MD; Andreas Früh, MD; Jan Elders, RN, MA; Anita Hiippala, MD; Gunter Kerst, MD; Roman A. Gebauer, MD; Peter Kubuš, MD; Patrick Frias, MD; Fulvio Gabbarini, MD; Sally-Ann Clur, MBBCh, MSc, FCP(SA)Paed, PhD; Bert Nagel, MD; Javier Ganame, MD; John Papagiannis, MD, PhD; Jan Marek, MD; Svjetlana Tisma-Dupanovic, MD; Sabrina Tsao, MD; Jan-Hendrik Nürnberg, MD; Christopher Wren, MD; Mark Friedberg, MD; Maxime de Guillebon, MD; Julia Volaufova, PhD; Frits W. Prinzen, MD, PhD; Tammo Delhaas, MD, PhD; for the Working Group for Cardiac Dysrhythmias and Electrophysiology of the Association for European Pediatric Cardiology

Background—We evaluated the effects of the site of ventricular pacing on left ventricular (LV) synchrony and function in children requiring permanent pacing.

Methods and Results—One hundred seventy-eight children (aged <18 years) from 21 centers with atrioventricular block and a structurally normal heart undergoing permanent pacing were studied cross-sectionally. Median age at evaluation was 11.2 (interquartile range, 6.3–15.0) years. Median pacing duration was 5.4 (interquartile range, 3.1–8.8) years. Pacing sites were the free wall of the right ventricular (RV) outflow tract (n=8), lateral RV (n=44), RV apex (n=61), RV septum (n=29), LV apex (n=12), LV midlateral wall (n=17), and LV base (n=7). LV synchrony, pump function, and contraction efficiency were significantly affected by pacing site and were superior in children paced at the LV apex/LV midlateral wall. LV dyssynchrony correlated inversely with LV ejection fraction (R=0.80, P=0.031). Pacing from the RV outflow tract/lateral RV predicted significantly decreased LV function (LV ejection fraction <45%; odds ratio, 10.72; confidence interval, 2.07–55.60; P=0.005), whereas LV apex/LV midlateral wall pacing was associated with preserved LV function (LV ejection fraction ≥55%; odds ratio, 8.26; confidence interval, 1.46–47.62; P=0.018). Presence of maternal autoantibodies, gender, age at implantation, duration of pacing, DDD mode, and QRS duration had no significant impact on LV ejection fraction.

Conclusions—The site of ventricular pacing has a major impact on LV mechanical synchrony, efficiency, and pump function in children who require lifelong pacing. Of the sites studied, LV apex/LV midlateral wall pacing has the greatest potential to prevent pacing-induced reduction of cardiac pump function. (***Circulation***. **2013;127:613-623.**)

Key Words: heart block ■ heart failure ■ pacemakers ■ pacing ■ pediatrics

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From the Children's Heart Center, University Hospital Motol, Prague, Czech Republic (J.J., S.K., P.K.); Department of Pediatric Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, Netherlands (I.E.v.G.); Evelina Children's Hospital, London, United Kingdom (E.R., K.N.); University Children's Hospital, Zurich, Switzerland (M.T.); Oslo University Hospital, Oslo, Norway (A.F.); Department of Cardiology, UMC St. Radboud, Nijmegen, Netherlands (J.E.); Department of Pediatric Cardiology, Children's Hospital, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland (A.H.); Pädiatrische Kardiologie, Universitätsklinik für Kindermedizin und Jugendmedizin, Tübingen, Germany (G.K.); Department of Pediatric Cardiology, University of Leipzig, Heart Centre, Leipzig, Germany (R.A.G.); Department of Pediatric Cardiology, Children's Hospital of Atlanta, Atlanta, GA (P.F.); Pediatric Cardiology Division, Children's Hospital Regina Margherita, Turin, Italy (F.G.); Emma Children's Hospital, Academic Medical Center, Amsterdam, and Center for Congenital Heart Anomalies Amsterdam/Leiden, Leiden, Netherlands (S.C.); Division of Pediatric Cardiology, Children's Hospital, Medical University Graz, Graz, Austria (B.N.); Department of Pediatric Cardiology, University Hospital Leuven, Leuven, Belgium (J.G.); Division of Pediatric Cardiology, Mitera Children's Hospital, Maroussi, Greece (J.P.); Department of Pediatric Cardiology, Great Ormond Street Hospital, London, United Kingdom (J.M.); Cardiology Section, Children's Mercy Hospitals and Clinics, Kansas City, MO (S.T.-D.); Division of Cardiology, Children's Memorial Hospital, Chicago, IL (S.T.); Klinikum Links der Weser, Abt Pediatric Cardiology, Bremen, Germany (J.N.); Department of Pediatric Cardiology, The Newcastle upon Tyne Hospitals, National Health Service Foundation Trust, Newcastle upon Tyne, United Kingdom (C.W.); Division of Cardiology, The Hospital for Sick Children, Toronto, Ontario, Canada (M.F.); Department of Congenital Heart Disease, Hôpital Cardiologique du Haut-Lévêque, Bordeaux University Hospitals, Bordeaux-Pessac, France (M.d.G.); Biostatistics Program, Louisiana State University Health Sciences Center, School of Public Health, New Orleans, LA (J.V.); Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, Netherlands (F.W.P); and Department of Biomedical Engineering, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, Netherlands (T.D.).

Correspondence to Jan Janoušek, MD, PhD, Children's Heart Center, University Hospital Motol, V Úvalu 84, 150 06 Prague 5, Czech Republic. E-mail jan.janousek@lfmotol.cuni.cz

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Right ventricular (RV) pacing has been used for decades in both adults and children. Recently, several large adult studies,[1–3] smaller pediatric reports,[4–7] and a larger pediatric survey[8] have pointed toward the adverse effects of RV pacing. The incidence of left ventricular (LV) dysfunction in RV paced children ranged within a median follow-up of less than a decade from 6.0% to 13.4%.[7] The impact of pacing-induced dyssynchrony may be especially important in children with a prospect of lifelong pacing that lasts for decades. This idea is furthered by findings that dyssynchronous LV activation causes pathological remodeling and dysfunction.[9] Pediatric pacemaker therapy represents an optimal model for the evaluation of the long-term effects of different pacing sites because, on the basis of surgical preferences and in contrast to adults, various pacing sites are used, including LV epicardial pacing. In small single-center reports[10–14] and a larger retrospective survey,[8] pacing from the LV apex or free wall was associated with better preservation of LV function. The purpose of the present multicenter study was to evaluate the influence of different ventricular pacing sites on long-term LV function in children with nonsurgical atrioventricular block and a structurally normal heart and to search for a mechanism for the difference in pump function between sites by measuring mechanical synchrony and efficiency in a cross-sectional echocardiographic evaluation.

Clinical Perspective on p 623

Methods

Recruitment and Demography

Patients were recruited from 21 centers providing pacemaker therapy for children (17 European and 4 North American) and had to fulfill the following inclusion criteria: presence of second- or third-degree atrioventricular block necessitating permanent cardiac pacing with >70% ventricular paced beats; age <18 years at the time of primary pacemaker implantation; absence of any but trivial structural heart disease and of any known systemic illness potentially influencing cardiac function; duration of pacing >1 year; and no change in the ventricular pacing site during the follow-up period. A total of 178 patients (female, 96; male, 82; complete atrioventricular block in 171) were included in the study, with a median age at pacemaker implantation of 3.2 years and interquartile range (IQR) of 0.2 to 7.0 years. Atrioventricular block was congenital in 138 patients and diagnosed later during childhood in the remaining 40. Maternal autoantibodies were present in 64 of the 136 mothers tested. Nine of the 178 patients had patent ductus arteriosus that was closed interventionally with the use of coils before (n=3), at the time of (n=3), or after (n=3) pacemaker implantation. The retrospectively gathered data additionally included demographic parameters, preimplantation LV size and function, New York Heart Association classification, and pacemaker implantation details (pacing site as recorded by the implanting physician; lead type [endocardial versus epicardial]; and initial pacing mode and its change during the follow-up period).

Cross-sectional Evaluation

After ethical approval by the hospital review committee and patient consent according to individual institutional guidelines were obtained, eligible patients were evaluated according to a prespecified protocol including New York Heart Association class assignment, 12-lead ECG, echocardiography, and, if not available in the patient files, a chest x-ray in the anteroposterior and lateral projections. The echocardiographic protocol consisted of the following: (1) 2-dimensional gray scale loops of the parasternal long-axis view, parasternal short-axis view (at the level of papillary muscles), and apical 4-chamber and 2-chamber views; 3 cardiac cycles were recorded in each view along with simultaneous ECG tracing to allow for identification of QRS onset; 3.5- and 5-MHz transducers with a minimal frame rate of 30 per second (ideally 60–90 per second) were used; (2) parasternal long-axis and short-axis M mode; and (3) pulsed Doppler of the RV outflow tract (RVOT) and LV outflow tract, pulsed transmitral Doppler, and qualitative assessment of mitral regurgitation (none=0, mild=1, moderate=2, and severe=3). Recordings were stored on CD/DVD as raw data from Vivid-GE systems and in Digital Imaging and Communications in Medicine format for other vendors.

Data Analysis

All data were analyzed in a core laboratory (Children's Heart Center, Prague, Czech Republic). First, QRS duration was measured manually as the maximum value in any lead from ECG printouts with a sweep speed of 25 or 50 mm/s. Second, approximate pacing site assignment was performed with the use of 12-lead ECG QRS morphology and axis and biplane chest x-rays to allow grouping into 7 categories for the purpose of statistical evaluation: free wall of the RVOT, lateral RV wall, RV apex, RV septum (any position), LV apex, lateral LV wall, and LV base. We used published algorithms for exact differentiation of the RV septal sites from the RVOT free wall sites.[15] Assignment to the RV lateral wall was performed in case of a leftward QRS axis along with left bundle-branch block morphology. RV and LV apical pacing were characterized by superior axis and left and right bundle-branch block morphology in lead I, respectively. Pacing was assigned to the LV lateral wall or LV base in case of a rightward QRS axis along with right bundle-branch block morphology with further differentiation according to the biplane x-ray. Third, the following echocardiographic analysis, measurements, and calculations were performed:

(1) LV dimensions were measured from the parasternal long-axis M-mode and expressed as *Z* scores with the use of weight-related normal limits.[16] LV shortening fraction was calculated.
(2) LV volumes were measured from the apical 4- and 2-chamber views with the Simpson biplane method. LV ejection fraction (EF) was calculated and graded as follows: normal (LV EF ≥55%), subnormal (LV EF <55%), and significantly decreased (LV EF <45%).
(3) Septal to posterior wall motion delay was measured from the parasternal short-axis M mode.[17] When maximum systolic motion was unclear, maximum systolic wall thickening was taken as the maximal excursion.
(4) Interventricular mechanical delay was calculated as the difference between LV and RV pre-ejection periods measured from QRS onset to the beginning of ventricular ejection with the use of pulsed Doppler from the RVOT and LV outflow tract.

Speckle tracking analysis was performed in 125 of 178 subjects with echocardiographic raw data available from Vivid-GE equipment (GE-Vingmed, Horten, Norway) with the use of an EchoPac workstation. Longitudinal segmental strain was calculated in the apical 4- and 2-chamber views and radial strain in the parasternal short-axis view according to standardized myocardial segmentation.[18,19] Each of the 3 recorded cardiac cycles was inspected visually with examination of both strain rate and strain curves, and the one with the least strain rate noise and unequivocally identifiable strain peaks was used for measurement. Segments automatically rejected by the software or those with unclear peaks were not used for analysis. Measurements were feasible in 938 of 1380 segments (68.0%) in the apical views and 625 of 660 segments (94.7%) in the short-axis view. Peak segmental systolic deformation timing, defined as the time from QRS onset to peak systolic strain, was measured in each segment. Subsequently, mechanical delays were calculated as the median time between peak systolic strain, as follows: (1) septal to lateral delay from the basal segments of the apical 4-chamber view; (2) anterior to inferior delay from the basal segments of the apical 2-chamber view; and (3) septal to lateral, anteroseptal to posterior, and anterior to inferior delays

from the parasternal short-axis view. Furthermore, a modified strain dyssynchrony index[20] was calculated. This index reflects wasted segmental contraction due to LV dyssynchrony. In brief, the difference between maximum and end-systolic strain (at the time of aortic valve closure as indicated by the end of systolic flow in the LV outflow tract) was measured in each segment and expressed as percentage of the respective maximum segmental strain. The proportion of wasted LV contraction was then calculated separately for the RV and LV pacing sites from the 12 LV segments in the apical 4- and 2-chamber views (basal, mid, and apical levels) and from the 6 segments in the parasternal short-axis view, respectively, as the sum of the segmental values divided by the number of segments. Wasted energy can result from premature end of shortening (maximum falls before aortic valve closure, as occurs in early-activated regions) or from postsystolic shortening (as occurs in late-activated regions). To ensure correct delineation of aortic valve closure, measurements were rejected if the difference between the cardiac cycle length of the aortic outflow Doppler and the respective speckle tracking measurement was >10%.

Statistical Analysis

If not otherwise stated, continuous data are presented as raw means (SDs). Differences in demographic and informative variables between pacing sites were evaluated by 1-way ANOVA with the use of the Holm-Sidak method for pairwise multiple comparisons or by the χ^2 test, as appropriate. The continuous outcome variables characterizing LV function and synchrony were analyzed with the use of a linear mixed model approach. Each model included the set of clinically informative additive covariates in addition to the main factor tested. The continuous covariates included age at implantation, pacing duration, and QRS duration. The dichotomous covariates were gender, presence of maternal antibodies, presence of congenital block, and DDD pacing. The main treatment factor included was the pacing site with 7 levels or a combination of specific pacing sites. In all models, the class variable "contributing center" was included as an additive random effect. For the random center effect, a simple covariance structure was assumed in all models. The statistical test of main treatment effect was an adjusted F test with Kenward-Roger type adjustment of denominator degrees of freedom. For the "site" main effect, multiple comparisons were performed with the use of the

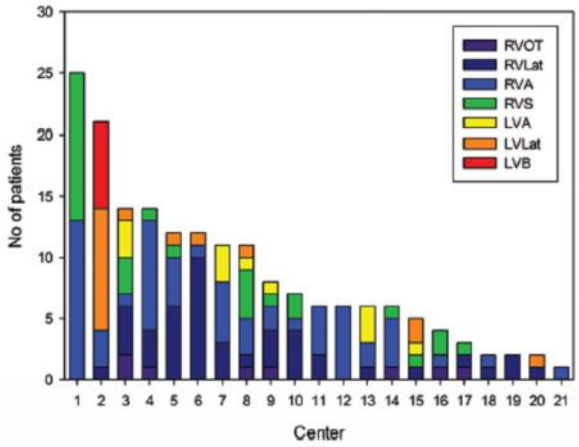

Figure 1. Number of patients and distribution of pacing sites per center (not corresponding with contributing center numbering). LVA indicates left ventricular apex; LVB, left ventricular base; LVLat, lateral left ventricular wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; and RVS, right ventricular septum.

Table 1. Demographic, Clinical, and Pacing Parameters According to Ventricular Pacing Site

Parameter	Pacing Site							Overall P	P<0.05 Between Groups
	RVOT [1]	Lateral RV Wall [2]	RV Apex [3]	RV Septum [4]	LV Apex [5]	Lateral LV Wall [6]	LV Base [7]		
No. of patients	8	44	61	29	12	17	7	…	…
Male, n (%)	7 (87.5)	21 (47.7)	33 (54.1)	11 (37.9)	1 (8.3)	6 (35.3)	3 (42.9)	0.016	…
CCAVB, n (%)	6 (75.0)	35 (79.5)	47 (77.0)	20 (69.0)	9 (75.0)	16 (94.1)	5 (71.4)	0.467	…
Maternal antibodies, yes/no/unknown, n (%)	5/3/0 (62.5/37.5/0)	16/22/6 (36.4/50/13.6)	19/27/15 (31.1/44.3/24.6)	12/13/4 (41.4/44.8/13.8)	7/2/3 (58.3/16.7/25)	5/3/9 (29.4/17.6/52.9)	0/2/5 (0/28.6/71.4)	0.644	…
LVEDD before implantation, Z score	1.64 (1.06)	1.81 (1.79)	1.79 (1.74)	2.11 (1.96)	1.71 (2.13)	1.49 (0.86)	1.53 (1.98)	0.980	…
LVSF before implantation, n (%)	42 (5)	38 (7)	41 (7)	43 (7)	40 (5)	42 (8)	41 (5)	0.359	…
LV EF before implantation, n (%)	65 (14)	66 (12)	62 (12)	61 (14)	68 (14)	60 (11)	64 (5)	0.632	…
Age at implantation, y	3.52 (5.61)	2.85 (3.64)	5.32 (4.29)	6.76 (5.43)	1.69 (2.50)	3.78 (4.61)	6.34 (6.32)	0.002	4 vs 2,5
Age at follow-up, y	7.02 (5.38)	9.73 (4.50)	12.62 (4.91)	12.78 (4.36)	4.08 (2.98)	10.08 (5.68)	11.72 (5.17)	<0.001	2 vs 3,4 vs 1,25 vs 2,3,4,6,7
Duration of pacing, y	3.51 (1.77)	6.87 (3.85)	7.31 (4.25)	6.02 (4.21)	2.38 (0.97)	6.30 (4.02)	5.39 (3.84)	0.002	5 vs 2,3
DDD pacing at follow-up, n (%)	6 (75.0)	11 (25.0)	33 (54.1)	16 (55.2)	6 (50.0)	10 (58.8)	6 (85.7)	0.007	…
QRS duration at follow-up, ms	143 (13)	157 (20)	157 (21)	146 (19)	127 (23)	158 (25)	177 (22)	<0.001	5 vs 2,3,6,77 vs 1,4
NYHA classification at follow-up	1.03 (0.17)	1.00 (0.00)	1.00 (0.00)	1.03 (0.19)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	0.628	…

Data are presented as number (percentage) or mean (SD). Numbers in square brackets and in the P value column refer to pacing site categories. CCAVB indicates congenital complete atrioventricular block; LVEDD, left ventricular end-diastolic dimension; LV EF, left ventricular ejection fraction; LVSF, left ventricular shortening fraction; NYHA, New York Heart Association; and RVOT, free wall of the right ventricular outflow tract.

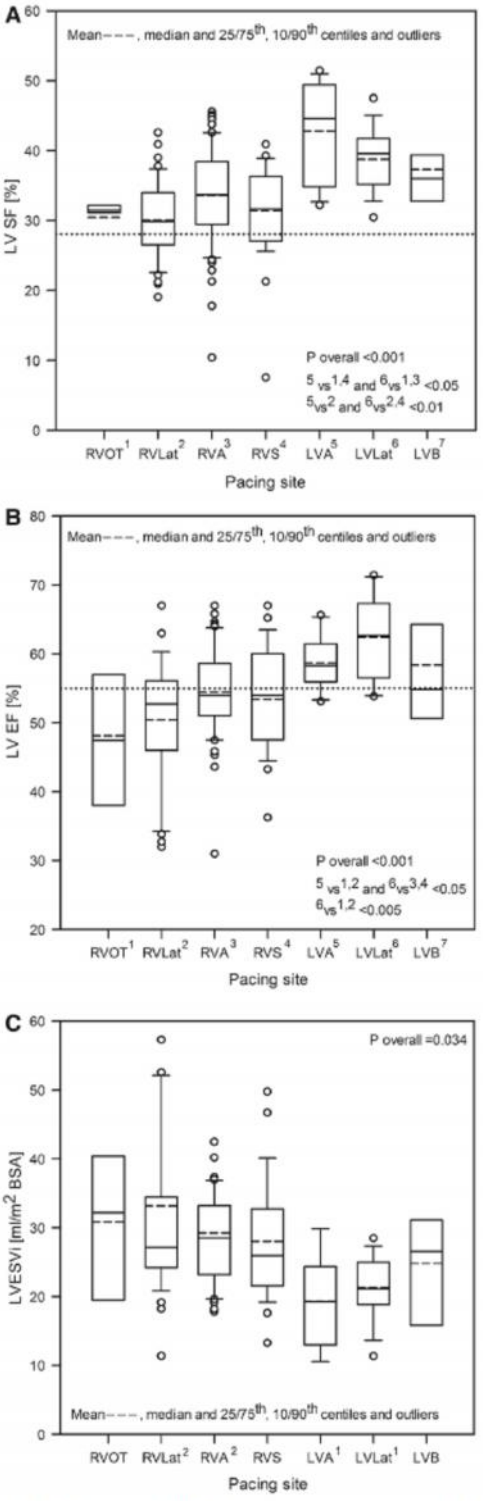

Figure 2. Left ventricular (LV) function at cross-sectional follow-up. **A**, LV shortening fraction (SF). **B**, LV ejection fraction (EF). **C**, LV end-systolic volume index (LVESVi). The dotted line shows the division between normal and subnormal values. LVA indicates LV apex; LVB, LV base; LVLat, lateral LV wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; and RVS, right ventricular septum.

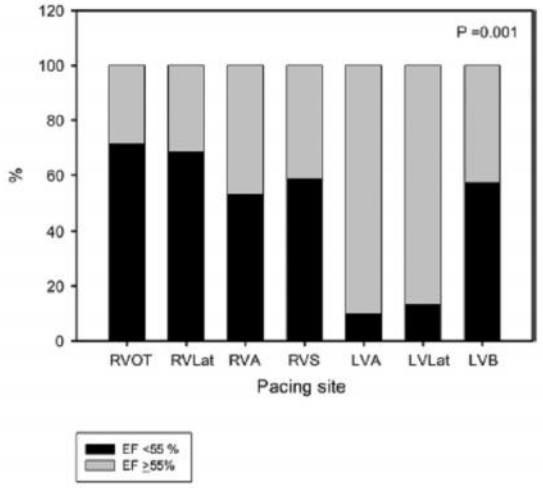

Figure 3. Proportion of patients with decreased left ventricular (LV) ejection fraction (EF) (<55%). LVA indicates LV apex; LVB, LV base; LVLat, lateral LV wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; and RVS, right ventricular septum.

Tukey-Kramer adjustment. The 2 dichotomous variables calculated from LV EF with a cutting point of 45% and 55%, respectively, were analyzed by a generalized mixed linear model. The distribution of the response was set to be binomial, and the probability of LV EF <45% (≥55%) was modeled by a log-link function. The covariates and main treatment effects were the same as for continuous variables. The data for dichotomous response are presented as odds ratios (95% confidence intervals). The difference in the modified strain dyssynchrony index between RV and LV pacing was evaluated by the Mann-Whitney rank sum test. Correlation between 2 continuous variables was evaluated by linear regression. Interobserver variability was tested by the coefficient of variation.[21] SigmaPlot for Windows

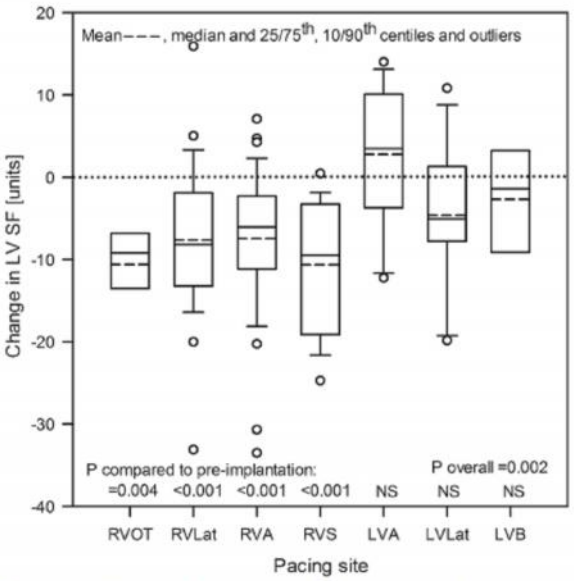

Figure 4. Change in left ventricular (LV) shortening fraction (SF) from preimplantation to cross-sectional follow-up. Dotted line indicates no change. LVA indicates LV apex; LVB, LV base; LVLat, lateral LV wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; and RVS, right ventricular septum.

Table 2. Comparison of LV Function Between RV Apical and LV Apical Plus Lateral Wall Pacing

	Pacing Site		
	RV Apex	LV Apex+Lateral LV Wall	*P*
n	61	29	
LVSF, %	34 (7)	40 (6)	0.0007
Change in LVSF, U (compared with preimplantation values)	−7 (9)	−1 (9)	0.044
LV EF, %	54 (6)	61 (6)	0.0015
LVESVi, mL/m² BSA	29 (9)	21 (5)	0.260

Data are presented as mean (SD). BSA indicates body surface area; EF, ejection fraction; LV, left ventricular; LVESVi, LV end-systolic volume index; LVSF, LV shortening fraction; and RV, right ventricular.

version 12.0 (Systat Software Inc, San Jose, CA) and SAS version 9.2 (SAS Institute Inc, Cary, NC) were used for statistical analysis. Significance was accepted at the $P \leq 0.05$ level.

Results

Cross-sectional evaluation was performed at a median age of 11.2 (IQR, 6.3–15.0) years. Median pacing duration was 5.4 (IQR, 3.1–8.8) years.

Pacing Sites

In total, 97 patients were paced epicardially and 81 from the endocardium. Patients were not distributed equally with respect to pacing site, reflecting the historical preference for RV pacing (Figure 1). Demographic and clinical parameters are summarized in Table 1. Patients paced from the LV apex were generally younger and had a shorter follow-up and QRS duration. In addition, gender distribution and the proportion of patients with DDD pacing were not equal.

LV Function

LV shortening fraction, biplane EF, and the end-systolic volume index (both available in 157 of 178 patients) were different between pacing sites, whereas the Z score of the LV end-diastolic dimension and the end-diastolic volume index did not differ. LV apex and lateral LV wall pacing yielded significantly higher shortening fraction and EF than did RV pacing sites (Figure 2). LV EF was not significantly different between RV septum and RV apex pacing. Patients with RVOT and lateral RV wall pacing had the largest scatter in LV EF, with the lower quartile as low as <38% in the RVOT group (Figure 2B). Patients with subnormal LV EF (<55%) were almost exclusively confined to RV pacing sites or LV base pacing, whereas the vast majority of patients paced from the LV apex or lateral wall had completely preserved LV function (Figure 3). Compared with preimplantation values, the decrease in LV shortening fraction was significant for all RV pacing sites and absent in the LV paced groups (Figure 4). Comparison of the best and clinically most commonly used RV site (ie, RV apex) with the combination of optimal LV sites (LV apex and lateral LV wall) still yielded a significant difference in favor of LV pacing (Table 2). To elucidate the potential effect of maternal autoantibodies, presence of congenital atrioventricular block, gender, age at implantation, pacing duration, DDD pacing, and QRS duration on LV function, these variables were introduced as covariates. Pacing site was the only significant predictor of both LV EF and shortening fraction ($P<0.0001$ for both), whereas none of the covariates reached significance. RVOT/lateral RV wall pacing was the only independent predictor of significantly decreased LV EF (<45%), whereas LV apex/lateral LV wall pacing was associated with preservation of LV function (LV EF ≥55%; Tables 3 and 4). To allow for comparison with a recent multicenter retrospective survey,[8] we also analyzed LV function by whether subjects were RV epicardial, RV endocardial, or LV paced. Results were similar to the previous findings,[8] with LV pacing being superior to RV endocardial or epicardial pacing in terms of LV shortening fraction, LV EF, and change in LV shortening fraction compared with preimplantation values (Table 5). No difference was found between RV apical epicardial and endocardial pacing.

LV Dyssynchrony

The interventricular and intra-LV delays were significantly different between pacing sites (Figure 5). LV EF and septal to posterior wall motion delay for the individual pacing sites are depicted in Figure 6. Segmental strain analysis by speckle tracking confirmed this mechanical dyssynchrony pattern (Figures 7, 8A, and 8B). RV pacing consistently produced delayed LV ejection and a mechanical contraction delay between the septum and LV free wall with the least negative effect of the RV

Table 3. Risk Factors for Decreased LV Function (LV EF <45%)

Variable in Model	LV EF <45%	LV EF ≥45%	*P*	Odds Ratio (95% CI)
Male gender, %	50.0	45.4	0.810	0.83 (0.18–3.81)
Congenital atrioventricular block, %	75.0	77.5	0.783	0.72 (0.07–7.42)
Maternal autoantibodies, %	61.5	43.6	0.406	2.51 (0.28–22.35)
Age at implantation, y	4.39 (4.79)	4.49 (4.66)	0.592	0.93 (0.72–1.21)
RVOT and lateral RV wall pacing, %	62.5	24.8	0.005	10.72 (2.07–55.60)
DDD pacing, %	50.0	48.2	0.520	1.77 (0.31–10.25)
Pacing duration, y	4.94 (3.32)	6.44 (4.13)	0.115	0.60 (0.75–1.06)
QRS duration, ms	154 (26)	154 (22)	0.477	1.02 (0.0.97–1.07)

Data are presented as percentage or mean (SD). CI indicates confidence interval; EF, ejection fraction; LV, left ventricular; RV, right ventricular; and RVOT, free wall of the RV outflow tract.

Table 4. Factors Associated With Preserved LV Function (LV EF ≥55%)

Variable in Model	LV EF ≥55%	LV EF <55%	P	Odds Ratio (95% CI)
Male gender, %	36.1	54.1	0.086	0.45 (0.18–1.12)
Congenital atrioventricular block, %	73.6	80.5	0.972	0.98 (0.29–3.35)
Maternal autoantibodies, %	41.1	49.3	0.103	0.37 (0.11–1.23)
Age at implantation, y	4.24 (4.46)	4.69 (4.83)	0.323	0.94 (0.82–1.07)
LV apical and lateral LV wall pacing, %	4.7	29.2	0.018	8.26 (1.46–47.62)
DDD pacing, %	45.8	50.6	0.455	1.50 (0.52–4.33)
Pacing duration, y	5.88 (3.78)	6.64 (4.30)	0.425	0.95 (0.84–1.08)
QRS duration, ms	149 (22)	158 (23)	0.593	0.99 (0.97–1.02)

Data are presented as percentage or mean (SD). CI indicates confidence interval; EF, ejection fraction; and LV, left ventricular.

apex pacing site. In contrast, during LV apex and lateral LV wall pacing, both interventricular and intraventricular dyssynchrony were minimal. Pacing sites located toward the LV base resulted in a reversed intra-LV dyssynchrony pattern with early free wall and late septal motion. LV EF was significantly dependent on the degree of LV dyssynchrony (Figure 8C).

Contraction Efficiency

The proportion of wasted LV contraction due to dyssynchrony measured by a modification of the strain dyssynchrony index[20] was significantly higher during RV pacing than during LV pacing for both radial and longitudinal systolic function, as follows: median 8.3% (IQR, 5.7–14.5%) versus 3.1% (2.2–3.5%) (P=0.002) and 6.2% (IQR, 5.0–8.2%) versus 2.1% (1.2–3.5%) (P<0.001), respectively.

Interobserver agreement (J.J., I.E.v.G.) was calculated in a total of 28 of 178 patients. Pacing site assignment was equal in 27 of 28 patients. The following coefficients of variation[21] were achieved in the parameters tested: biplane LV EF=9.7%, interventricular mechanical delay=5.7%, septal to posterior wall motion delay=11.2%, and intersegmental mechanical delay from 2-dimensional strain=0.9%.

Discussion

This is the first cross-sectional multicenter study showing significant differences between various ventricular pacing sites in terms of LV synchrony, function, and contraction efficiency in a large group of children who are chronically paced for complete atrioventricular block in the absence of structural heart disease. The results can be summarized as follows:

(1) LV apical and LV lateral wall pacing are associated with the best preservation of LV function, which appears to be related to preserved mechanical synchrony and contraction efficiency.
(2) RV pacing sites carry a high risk for a negative effect on LV performance, coinciding with significant mechanical asynchrony and contraction inefficiency. This effect is most pronounced for RV lateral and RVOT pacing and less pronounced for RV apical pacing.
(3) Nontargeted RV septal pacing does not show any advantage over RV apical pacing.
(4) LV basal pacing produces a significantly reversed pattern of LV dyssynchrony and should probably not be the preferred LV pacing site.
(5) The presence of maternal autoantibodies is not associated with decreased LV function and could not be confirmed as a modifier of the response to pacing-induced LV dyssynchrony.

This study strongly supports previous findings of a retrospective pediatric report[7] showing a decrease in LV function specifically due to RV free wall pacing. Our results also confirm data on preservation of LV function with LV apical or LV lateral wall pacing,[10–14] including a large retrospective pediatric multicenter survey[8] and a recently published experimental study.[22] Our present report does not show any superiority of RV septal over RV apical pacing. This is in agreement with another experimental work published by Mills et al[23] a few years ago. Some clinical studies showed promising results with the use of RV septal lead placement,[24] but clear benefit from RV septal pacing has not yet been demonstrated in a randomized trial, except when the lead is positioned in the His bundle.[25]

RV pacing (in contrast to LV pacing) was associated with depressed systolic function and induced a consistent decrease in LV systolic function compared with preimplantation values. This decrease was functionally well tolerated because no difference in New York Heart Association class was observed between the pacing sites. However, given the cross-sectional design of the study, patients suffering from symptomatic heart

Table 5. Differences Between RV Epicardial, RV Endocardial, and LV Pacing

	Pacing Site			P	
	RV Epicardial [1]	RV Endocardial [2]	LV [3]	Overall	Between Groups
LVSF, %	31 (5)	33 (7)	40 (6)	<0.0001	<0.001, 1,2 vs 3
Change in LVSF, SF units	−9 (9)	−8 (9)	−1 (9)	0.023	0.0235, 2 vs 3
LV EF, %	52 (8)	53 (7)	60 (6)	<0.0001	<0.001, 1,2 vs 3

Data are presented as mean (SD). Numbers in square brackets and in the P value column refer to pacing site categories. EF indicates ejection fraction; LV, left ventricular; LVSF, LV shortening fraction; and RV, right ventricular.

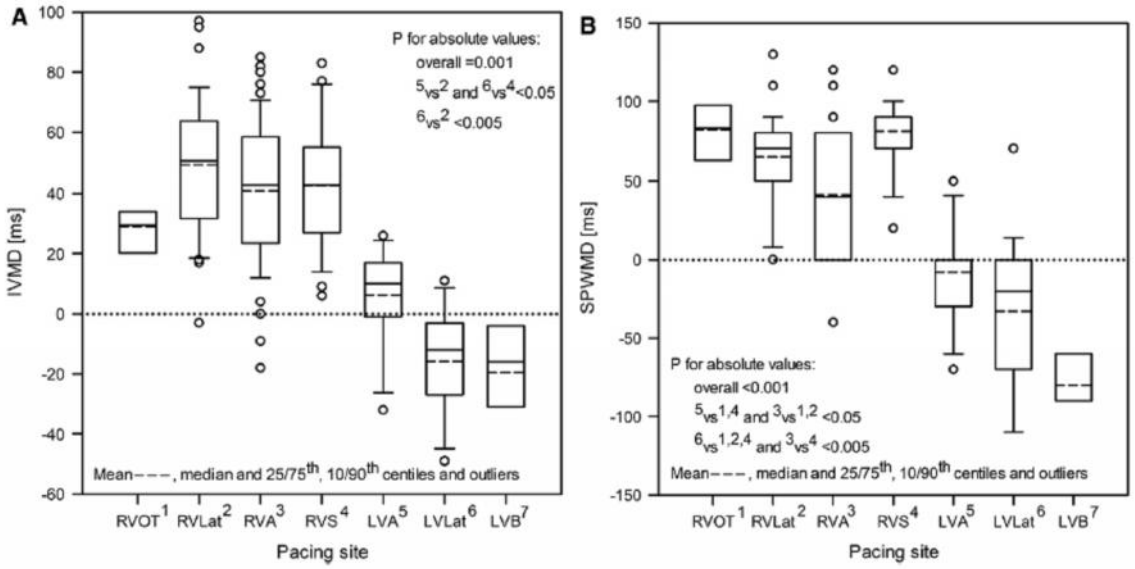

Figure 5. **A**, Interventricular mechanical delay (IVMD). **B**, Septal to posterior wall motion delay (SPWMD). To allow for comparisons between pacing sites, statistical significance is calculated for absolute measurement values. Dotted line indicates interventricular/intraventricular synchrony. LVA indicates left ventricular apex; LVB, left ventricular base; LVLat, lateral left ventricular wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; and RVS, right ventricular septum.

failure may have been missed because they were upgraded to a biventricular system, were transplanted, or died. The incidence of patients suffering from heart failure due to RV pacing has been reported to range from 6.0% to 13.4% in previous pediatric reports.[5–7]

Results of this study further indicate that LV pacing may be a substitute for primary biventricular pacing, which has recently been shown to preserve LV function in chronically paced adults.[26] As demonstrated by Tomaske et al[27] and Vanagt et al[28] in small descriptive pediatric reports, LV pacing may also be used instead of biventricular pacing to improve LV function that has been compromised from long-term RV pacing.

QRS duration was not a multivariable predictor of decreased LV function because it reflects the total electric activation time but not the sequence of activation. Recently, a subanalysis of

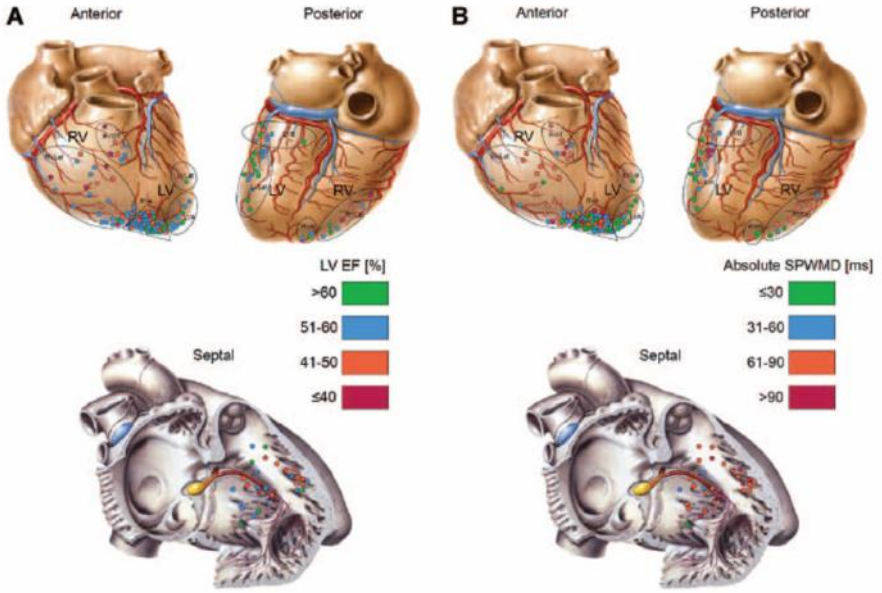

Figure 6. Approximate pacing sites as assessed from biplane chest x-rays and 12-lead ECG and color-coded absolute values of left ventricular (LV) ejection fraction (EF) (**A**) and septal to posterior wall motion delay (SPWMD) (**B**) in each specific patient. RV indicates right ventricle. Adapted with permission from Netter FH. *Atlas of Human Anatomy*. 2nd ed. Hansen JT, consulting ed. Teterboro, NJ: Icon Learning Systems; 1997; plates 205 and 213 (pacing sites are not part of the original image and were added by the authors).

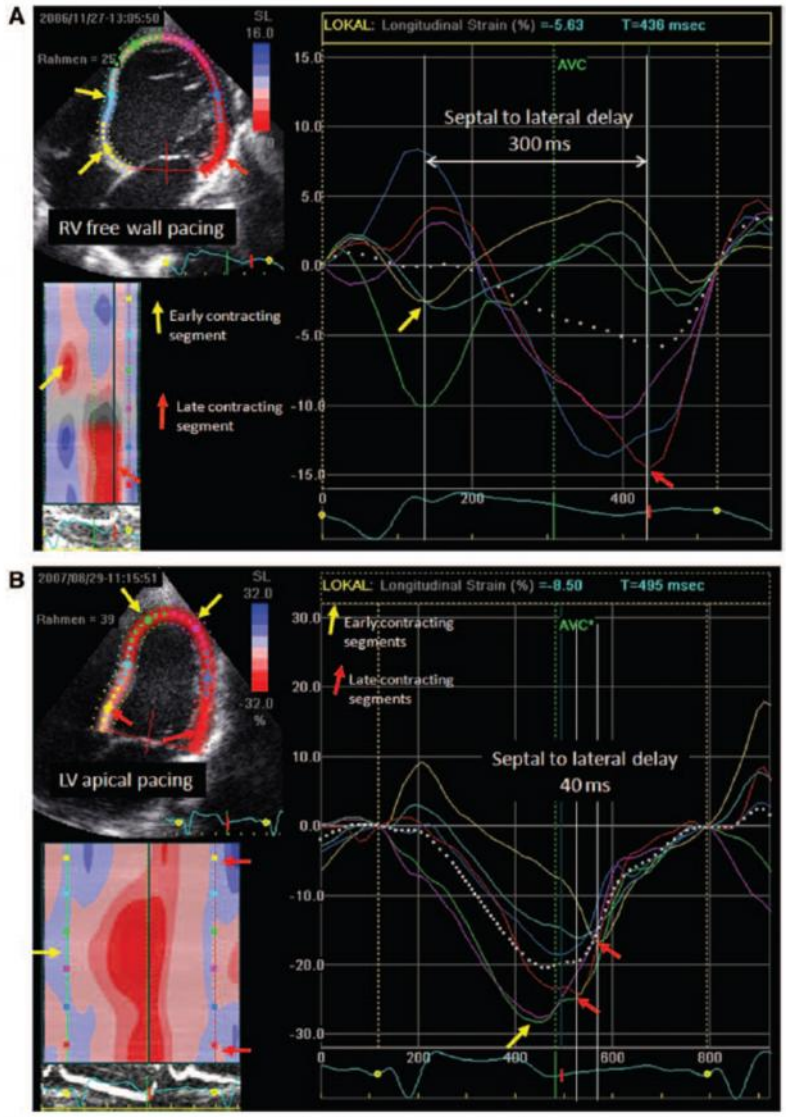

Figure 7. **A**, Mechanical activation pattern in right ventricular (RV) free wall pacing showing early peak negative 2-dimensional strain in the basal and midventricular septum (**yellow arrow**) and late negative strain peak in the left ventricular (LV) free wall (**red arrow**). An extensive septal to lateral mechanical dyssynchrony with a delay of 300 ms is present. **B**, LV apical pacing with mechanical activation starting at the apex (yellow arrows) and proceeding to the base (**red arrows**), resulting in almost complete septal to lateral mechanical synchrony.

the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) has shown that left bundle-branch block morphology rather than QRS duration is the prerequisite for the efficacy of cardiac resynchronization therapy.[29] This implies that a specific activation pattern is more important than total asynchrony. Our study indicates that the negative effects of LV dyssynchrony produced by RV pacing are preventable by LV pacing irrespective of QRS duration.

The presence of maternal autoantibodies in the setting of congenital atrioventricular block was not found to be a component of individual reactivity to pacing-induced LV dyssynchrony as opposed to a study showing association of autoimmune atrioventricular block with dilated cardiomyopathy.[30] None of the patients who were paced from the LV showed decreased LV function, despite the presence of maternal autoantibodies in a significant portion. RV pacing–induced LV dysfunction has been reported previously in the absence of maternal autoantibodies in children with surgical atrioventricular block and could be effectively corrected by an upgrade to biventricular pacing.[31,32] All of these findings support our statement that the pacing site plays a crucial role in the development of pacing-associated LV dysfunction.

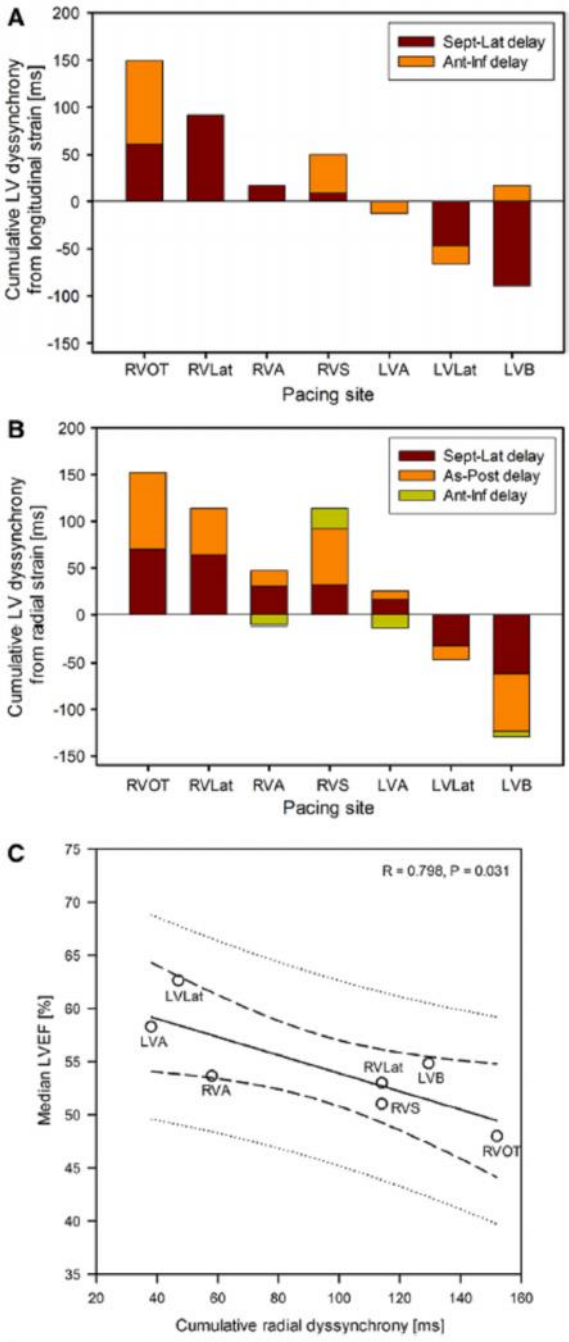

Figure 8. Cumulative left ventricular (LV) dyssynchrony with the use of longitudinal strain in apical 4- and 2-chamber views (**A**) and with the use of radial strain in the parasternal short-axis view (**B**). **C**, Relationship between the degree of cumulative LV dyssynchrony with the use of radial strain and LV ejection fraction (EF). Ant-Inf delay indicates anterior to inferior delay; As-Post delay, anteroseptal to posterior delay; LVA, left ventricular apex; LVB, LV base; LVLat, lateral LV wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; RVS, right ventricular septum; and Sept-Lat delay, septal to lateral delay.

Study Limitations

This study has limitations related to the unequal number of patients in each pacing site group, significant differences in age at primary implantation, and duration of pacing, as well as the accuracy of the retrospective assessment of the pacing site with the use of surgical records, biplane x-ray, and 12-lead ECG. However, neither age nor duration of pacing was a multivariable predictor of LV dysfunction, and pacing site localization could be performed with acceptable interobserver variability. In addition, there is some degree of uncertainty about the exact proportion of fully captured paced beats during the entire pacing period. However, the vast majority of patients had complete atrioventricular block (171/178) with a low probability of spontaneous rhythm. Moreover, all available 12-lead ECGs showed a permanently paced rhythm in all cases. The lack of atrioventricular synchrony as present in the patients with VVI(R) pacing may have been another confounder. The pacing mode was, however, not a factor influencing LV function in any of the analyses performed. Additionally, biplane LV EFs were not available in all patients. The differences between pacing sites, however, could be confirmed by the analysis of LV shortening fractions. In addition, the study protocol did not include RV evaluation, and potentially negative effects of LV pacing on RV function could therefore not be assessed. One of the legitimate statistical concerns is that a certain bias in the analysis of the mean response is introduced because the patients were not randomized with respect to pacing sites. However, in our approach we addressed this limitation by including all available confounders in all analyzed models as covariates. Propensity score adjustment might be considered an alternative approach. We have not applied it here because the basic assumption for the propensity score analysis, that no additional confounders exist other than those collected on patients, was not verifiable.

Conclusions

The site of ventricular pacing has a major impact on LV mechanical synchrony, efficiency, and pump function in children who require lifelong pacing. Of the sites evaluated in the present study, LV apex/lateral LV wall pacing has the greatest potential to prevent pacing-induced reduction of cardiac pump function, whereas RVOT/lateral RV wall pacing is associated with a high risk of LV dysfunction. Although it is associated with a mild decrease in LV EF in approximately one half of the patients, RV apex pacing is well tolerated in the majority. These data may guide clinicians in selecting proper pacing strategies in a population that will be subjected to several decades of permanent cardiac pacing and in which the aim to optimally preserve LV synchrony and function should be mandatory. Surgical access to the LV is possible with the use of existing tools and at no additional cost: the subxiphoid approach in younger children or, in older ones, a left lateral thoracotomy with an excellent cosmetic result.[33] The results of the present study also provide an important clinical confirmation of previously published experimental research.[22,23,34,35]

Sources of Funding

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CLINICAL PERSPECTIVE

Permanent cardiac pacing that starts in childhood will continue for decades. The observed reduction in left ventricular (LV) function in right ventricular–paced children is only the beginning of a process that will likely develop further over subsequent decades. Thus, the aim to preserve LV synchrony and function should be mandatory. The site of ventricular pacing has a major impact on LV mechanical synchrony, efficiency, and pump function in children who require lifelong pacemaker therapy. These clinical findings have provided an important confirmation of previously published experimental research. Pediatric patients with a systemic LV who are scheduled for epicardial lead implantation should be paced from the LV apex or free wall, whereas the right ventricular free wall and outflow tract should be avoided. Transvenous leads may still be placed in the right ventricular apex given that it had the least negative hemodynamic influence of all right ventricular pacing sites. These patients, however, should be monitored for changes in ventricular performance. The mentioned principles may be applied to all children with a systemic LV and either spontaneous or surgical atrioventricular block. Care should be taken to place the leads at the LV apex rather than the LV base because the inverse pattern of electromechanical dyssynchrony caused by LV basal pacing might be detrimental in the long term. Given the fast developments in pacemaker technology and the expected introduction of leadless pacing systems with a potential for an easy application of LV pacing, our findings may also have importance for the future strategy of pacemaker therapy in adults.

6. Diskuse

Kardiostimulace u dětí má svá specifika vyplývající z řady faktorů, z nichž nejdůležitějšími jsou věk pacientů, fyzický růst, častá přítomnost strukturální vrozené srdeční vady, omezený žilní přístup do srdce (malý průsvit cévy, případně anatomické cévní anomálie) a riziko žilní trombózy (v přítomnosti stimulační elektrody). Rychlý technický rozvoj jednotlivých komponent stimulačního systému (mj. nových typů epikardiálních stimulačních elektrod), spojený s jejich příznivějším dlouhodobým přežíváním/funkčností, významně zvýšil možnosti ochrany cévního přístupu do srdce odložením nutnosti transvenózního zavedení stimulačních elektrod do vyššího věku. Epikardiální přístup je dále spojen s významně větší možností výběru stimulačního místa, než je tomu v případě transvenózní stimulace, rutinně používané u dospělých pacientů a starších dětí (s absencí komplexní strukturální srdeční vady). Vzhledem ke skutečnosti, že konvenční stimulace subpulmonální komory vede v důsledku elektromechanické dyssynchronie u části pacientů k rozvoji dysfunkce systémové komory (stimulací indukovaná kardiomyopatie), patří nalezení stimulačního místa, u kterého by bylo riziko selhání systémové komory eliminováno nebo významně sníženo, mezi zásadní priority v oblasti trvalé kardiostimulace. Výběr stimulačního místa by měl být veden úvahou o hemodynamických důsledcích chronické stimulace, zejména v situaci, kdy předpokládaná doba této terapie dosahuje desítek let.

Dlouhodobé přežívání epikardiálních stimulačních elektrod bývalo v minulosti významně nižší v porovnání s elektrodami transvenózními, zejména u dětských pacientů a v přítomnosti vrozené strukturální srdeční vady.[84] Zavedením epikardiálních elektrod s postupným uvolňováním steroidů byly výhody transvenózních elektrod ve smyslu vývoje stimulačního prahu a přežívání generátoru kardiostimulátoru prakticky eliminovány.[85,86]

Některé vlastnosti epikardiálních elektrod byly do jisté míry dány jejich unipolárním charakterem (vyšší stimulační práh, nižší impedance elektrody, větší odběr proudu a nižší přežívání generátoru).[84] Naše studie jako první prokázala větší přežívání (ve smyslu absence nutnosti chirurgické reintervence) v pediatrické praxi nejčastěji používaného typu bipolárních stimulačních elektrod v porovnání s unipolárními elektrodami téhož výrobce. Důvodem je robustnější design bipolárních elektrod a zejména možnost přepnutí polarity stimulace z bipolární do unipolární v případě poškození zevního vodiče elektrody. Dále jsme pozorovali významné zvýšení celkové pravděpodobnosti setrvalé epikardiální stimulace (absence nutnosti konverze na částečný či úplný transvenózní stimulační systém) v recentní implantační periodě (po r. 2000). Rovněž v multivariátní analýze byla recentní implantační éra (kromě mužského pohlaví) jediným faktorem ovlivňujícími nutnost konverze na transvenózní systém. Věk pacientů v době implantace nebyl z tohoto hlediska významným faktorem a tedy i malé děti profitovaly z epikardiálního přístupu ve smyslu absence nutnosti časné konverze na transvenózní stimulační systém.

Použití moderních bipolárních steroidních elektrod a specifické programovatelné funkce zaměřené na snížení stimulační energie (AutoCapture™) byly ve shodě s dříve publikovanými daty[85,87] identifikovány jako významné faktory pozitivně ovlivňující životnost baterie kardiostimulátoru. Potvrdili jsme nálezy předchozích prací[88,89] uvádějících několikanásobné snížení rizika poruchy elektrody charakteru exit bloku při použití steroidních elektrod.

Oproti dosavadním studiím umožnily naše další práce posoudit dlouhodobý vliv řady specifických stimulačních míst na rozvoj stimulací indukované kardiomyopatie. Mezinárodní průřezová observační studie zahrnula dosud největší počet dětí se strukturálně normálním srdcem vyžadujících trvalou antibradykardickou stimulaci a je první svého druhu, poukazující

na významné rozdíly vlivu stimulačního místa na mechanickou synchronii a funkci LK u těchto pacientů. Ve shodě s předchozími studiemi zaměřenými na patofyziologický podklad stimulací indukované dyssynchronie[12,25,55,56,78] a rovněž ve shodě s předchozími klinickými studiemi[90,91,92] jsme prokázali významný vliv místa stimulace na parametry mechanické synchronie a systolické funkce LK, přičemž jako optimální, stran zachování těchto parametrů, se z dlouhodobého hlediska jeví stimulace hrotu LK, případně její volné stěny. Stimulace volné stěny PK byla naopak, v souladu s dříve publikovanou studií,[60] nejvíce spojena s rozvojem dyssynchronie kontrakce a snížením funkce LK u pacientů v porovnání s dobou před zavedením kardiostimulace. Ve shodě s dříve publikovanou studií[93] jsme rovněž neprokázali výhodnost necílené stimulace interventrikulárního septa PK oproti hrotu PK. Výsledky naší studie poukazují na možnost stimulace LK jako možné alternativy k primárně biventrikulární stimulaci, která bývá často zvažována v rámci prevence stimulací indukované kardiomyopatie u dospělých pacientů vyžadujících chronickou kardiostimulaci.[94]

V konečném důsledku naše studie vedou k jednoznačnému doporučení použití hrotu LK, případně její volné stěny, pro antibradykardickou stimulaci u dětí s perspektivou doživotní kardiostimulace (u kterých je zvažován epikardiální přístup při jejím zavedení), a to nezávisle na etiologii atrioventrikulární blokády (vrozená nebo chirurgická po předchozí operaci strukturální srdeční vady). Volná stěna pravé komory a její výtokový trakt jsou naopak nevhodnými místy z hlediska dlouhodobého zachování funkce LK. Stimulace bazální stěny LK vede k obrácenému obrazu aktivace LK (s časnou aktivací volné stěny LK a opožděnou kontrakcí septa) a neměla by tedy být upřednostňována před stimulací hrotu LK. U transvenózních elektrod je hrot PK přijatelným místem stimulace, avšak vyžadujícím dlouhodobé pravidelné sledování funkce LK.

Je pravděpodobné, že naše práce mohou v budoucnu přispět i ke tvorbě strategie při trvalé kardiostimulaci u dospělých pacientů, zejména v souvislosti s některými nově se objevujícími možnostmi techniky trvalé kardiostimulace (leadless pacing apod.).

Výsledky studií, které jsou součástí této disertační práce, byly zahrnuty do několika mezinárodních doporučení týkajících se přístupu k dětským pacientům se srdečním selháním[95] nebo poruchami rytmu[96] a dospělým pacientům s vrozenou srdeční vadou.[97]

7. Závěr

Provedenými studiemi jsme potvrdili hypotézy této práce.

1. Pravděpodobnost trvání epikardiální stimulace je u dětí – s využitím modernizovaných komponent stimulačních systémů a specifických programovatelných funkcí kardiostimulátorů - vysoká a umožňuje odsunout nutnost zavedení transvenózní stimulace do významně vyššího věku.
2. Chronická konvenční stimulace ze subpulmonální pravé komory, zejména její volné stěny a výtokového traktu, je spojena s významnější elektromechanickou dyssynchronií a vyšším rizikem rozvoje stimulací indukované kardiomyopatie. Naproti tomu hrot (případně volná stěna) levé komory je vhodným místem pro trvalou stimulaci komor u dětí a jeho využitím lze významným způsobem omezit riziko vzniku stimulací indukované kardiomyopatie.

8. Souhrn

Resynchronizace a prosynchronizace u trvalé kardiostimulace u dětí

Cíle:

1. Zhodnocení dlouhodobých výsledků trvalé epikardiální stimulace v dětském věku
2. Zhodnocení klinického vlivu elektromechanické dyssynchronie u trvalé kardiostimulace v dětském věku
3. Nalezení optimálních stimulačních míst pro trvalou kardiostimulaci u dětí ve smyslu zachování synchronie a funkce levé komory a minimalizace rizika stimulací indukované kardiomyopatie

Metody:

1. Retrospektivní observační studie na zhodnocení dlouhodobých výsledků trvalé epikardiální kardiostimulace v dětském věku v České republice s ohledem na výskyt dlouhodobých komplikací a stimulací indukované dysfunkce systémové komory a její léčbu pomocí srdeční desynchronizace.
2. Mezinárodní multicentrická průřezová studie na zhodnocení dlouhodobého efektu jednotlivých stimulačních míst v pravé a levé komoře na mechanickou synchronii a funkci levé komory u dětí (< 18 let) s permanentní antibradykardickou stimulací pro úplnou atrioventrikulární blokádu a strukturálně normálním srdcem.

Výsledky:

1. Celková pravděpodobnost setrvalé epikardiální stimulace (absence nutnosti konverze na částečný či úplný transvenózní stimulační systém) v dětském věku byla 92,8/76,1

% po 5/10 letech kardiostimulace, a zvýšila se v recentní implantační periodě (po r. 2000) ze 71,5 na 86,8 % po 9 letech od implantace (P = 0,040). Známky dyssynchronního srdečního selhání nebyly přítomny u žádného z pacientů, kteří měli iniciálně stimulaci ze systémové komory.

2. Ejekční frakce a frakce zkrácení LK byly významně vyšší při stimulaci hrotu LK a laterální stěny LK než při stimulaci z různých míst PK. Stimulace výtokového traktu pravé komory (RVOT) a laterální stěny PK naopak vedly k nejnižším zaznamenaným hodnotám EF. Subnormální (< 55 %) EF LK byla dokumentovaná téměř výhradně u pacientů stimulovaných z PK nebo báze LK. Naopak, většina pacientů se stimulací hrotu a laterální stěny LK měla normální EF LK (≥ 55 %). Významný pokles EF LK (v porovnání s hodnotami před implantací stimulačního systému) byl zaznamenán u všech stimulačních míst PK, ale u žádného na LK.
3. Místo stimulace bylo jediným významným (P < 0,0001) prediktorem frakce zkrácení a EF LK. Stimulace RVOT/laterální stěny PK byla jediným významným prediktorem významně snížené EF LK (ejekční frakce LK < 45 %, OR = 10,72, 95% CI 2,07 – 55,60, P = 0,005), zatímco stimulace z hrotu LK/mid-laterální stěny LK byla spojena se zachováním funkce LK (ejekční frakce LK ≥ 55 %, OR = 8,26, 95% CI 1,46 – 47,62, P = 0,018). Nebyly shledány rozdíly ve sledovaných parametrech funkce LK při stimulaci hrotu PK epikardiálně a endokardiálně.

Závěr:

1. Pravděpodobnost dlouhodobého trvání epikardiální stimulace je u dětí vysoká a účinně odsouvá nutnost transvenózní stimulace do vyššího věku.

2. Chronická stimulace pravé komory, zejména její volné stěny a výtokového traktu, je spojena s vyšším rizikem rozvoje dysfunkce levé komory v důsledku elektromechanické dyssynchronie. Stimulace hrotu levé komory (případně její volné stěny) naopak vede v největší míře k zachování funkce levé komory a prevenci vzniku stimulací indukované kardiomyopatie.

Summary

Resynchronization and prosynchronization in permanent cardiac pacing in children

Objectives:

1. To evaluate results of permanent epicardial pacing in children
2. To evaluate clinical impact of electromechanical dyssynchrony in permanent cardiac pacing in children
3. To identify the pacing sites with the greatest potential to prevent pacing-induced cardiomyopathy.

Methods:

1. Retrospective observational study on the long-term results of permanent epicardial pacing in children in the Czech Republic, factors modifying pacing system survival and the incidence of pacing-induced reduction of cardiac pump function.
2. Multi-centre cross-sectional study on long-term effects of the site of ventricular pacing on left ventricular synchrony and function in children with complete atrioventricular block and structurally normal heart requiring permanent pacing.

Results:

1. Overall probability of continued epicardial pacing (absence of change to a partial or total transvenous system) was 92.8 and 76.1% at 5 and 10 years after implantation, respectively, and increased in the recent implantation era (2000 and later) from 71.5 to 86.8% at 9 years (P = 0.040). None of those patients who were paced from the systemic ventricle showed signs of dyssynchronous systemic ventricular failure.

2. Left ventricular (LV) apex and LV lateral wall yielded significantly higher ejection fraction (EF) and shortening fraction (SF) than did right ventricular (RV) pacing sites. Patients with subnormal LV EF (< 55%) were almost exclusively confined to RV pacing sites or LV base. On the contrary, the vast majority of patients paced from LV apex or LV lateral wall had preserved LV EF (≥ 55%). If compared with pre-implantation values, the decrease in LV SF was significant in all RV pacing sites, and was absent in the LV-paced groups.
3. Pacing site was the only significant predictor of LV EF and LV SF ($P < 0.0001$ for both). Right ventricular outflow tract/RV lateral wall pacing was the only predictor of significantly decreased LV EF (LV EF < 45%, OR = 10.72, 95% CI 2.07 – 55.60, P = 0.005) whereas LV apical/lateral wall pacing preserved LV EF (LV EF ≥ 55%, OR = 8.26, 95% CI 1.46 – 47.62, P = 0.018). There was no difference between RV apical epicardial and endocardial pacing.

Conclusion:

1. Permanent epicardial pacing in children has a favorable outcome in terms of pacing system survival probability and potential for sparing the venous access to the heart in young individuals with the perspective of decades of pacing.
2. In permanent cardiac pacing, RV pacing sites (especially outflow tract and lateral wall) have the highest negative impact on LV electromechanical synchrony and pump function. Left ventricular apex and lateral wall are the optimal pacing sites minimizing the risk for pacing-induced cardiomyopathy.

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10. Seznam zkratek

PK: pravá komora

LK: levá komora

EF: ejekční frakce

SRL: srdeční desynchronizační léčba

AV: atrioventrikulární

IVS: interventrikulární septum

NYHA: New York Heart Association

IVMD: interventricular mechanical delay

SPWMD: septal to posterior wall motion delay

SLMD: septal to lateral mechanical delay

RVOT: výtokový trakt pravé komory

SF: shortening fraction

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