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# Optimal site cardiac pacing in children

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Introduction:

Right ventricular (RV) pacing is associated with asynchronous left ventricular (LV) activation, which can lead to deleterious pathological remodeling 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. The main aim of this study was to evaluate the effects of the site of ventricular pacing on left ventricular (LV) synchrony and function in children requiring permanent pacing.

Methods and results:

Linear mixed model are statistical models for continuous outcome variables in which the residuals are normally distributed but may not be independent or have constant variance. Linear mixed model is suitable for clustered, longitudinal, or repeated-measures data. It may include both fixed effect parameters associated with one or more continuous or categorical covariates and random factors. The fixed-effect parameters describe the relationships of the covariates to the dependent variable for an entire population, and the random effects are specific to subjects within a population.

The matrix form of a linear mixed model in general:

$$Y = X\beta + ZU + \varepsilon,$$

(1) $Y$ is an $n$ dimensional response vector;
(2) $\beta$ is a vector of $m$ unknown regression coefficients for fixed explanatory variables,
(3) $U$ is a vector of random effects, $U \sim N_p(0, \sigma^2 I)$;
(4) $X$ (design matrix $n\ x\ m$) and $Z$ (design matrix $n \times p$);
(5) $\varepsilon$ is a vector of random errors, $\varepsilon \sim N_n(0, \sigma^2 R)$;
(6) $U$ and $\varepsilon$ are independent.

Data:

178 children (age <18 years) from 21 Centers (17 European and four North American) with atrioventricular block and a structurally normal heart undergoing permanent pacing were investigated. Mean (standard deviation) of age at follow up and pacing duration was 10. (5.2) and 6.3 (4.1) years, respectively. Pacing-sites were the free wall of the right ventricular (RV) outflow tract (RVOT, N=8), lateral RV (RVLat, N=44), RV apex (RVA, N=61), RV septum (RVS, N=29), LV apex (LVA, N=12), LV mid-lateral wall (LVLat, N=17), and LV base (LVB, N=7). Summarization for data is shown in Table 1. Data are presented as mean (SD) or as median (25/75% quartiles). For comparison in Table 1 are parametric tests used.

Statistical analysis:

The response in this model is the left ventricular ejection fraction (LVEF). In cardiovascular physiology, ejection fraction represents the volumetric fraction of blood pumped out of the ventricle (heart) with each heart beat or cardiac cycle. 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. (QRS is the name for the combination of three of the graphical deflections seen on a typical electrocardiogram. It is usually the central and most visually obvious part of the tracing.) 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 (Figure 2) with seven levels or a combination of specific pacing sites: free wall of the RV outflow tract (RVOT), lateral RV wall (RVLat), RV apex (RVA), RV septum (RVS) (any position), LV apex (LVA), lateral LV wall (LVLat), and LV base (LVB). The class variable "Contributing center" was included as an additive random effect in each model. For the random "Center" effect a simple covariance structure was assumed. The statistical test of main treatment effect was an adjusted F-test. For the "Pacing site" main effect, multiple comparisons were performed using the Tukey-Kramer adjustment. REML is used as the estimation methods for the covariance parameters in mixed model.

Statistical software package SAS Version 9.3 (SAS Institute, NC, USA) and R version 2.15.1 were used for all statistical analysis. Significance was accepted at 0.05 level.

Conclusion:

Age at implantation, pre-implantation LV size and function, duration of pacing, DDD mode, QRS duration, and presence of maternal auto-antibodies had no significant impact on LVEF. The site of ventricular pacing has a major impact on LV efficiency in children that require life-long pacing. LVA/LVLat pacing allows for optimal prevention of pacing-induced heart failure.

References:
[1] Ramon C. Littell, George A. Milliken, Walter W. Stroup, Russell D. Wolfinger, Oliver, Ph.D. Schabenberber: SAS for Mixed Models. Second Edition. SAS Inst. 2006.
[2] Roman A. Gebauer, Viktor Tomek, Petr Kubuš, Vít Rázek, Tomáš Matějka, Aida Salameh, Martin Kostelka, and Jan Janoušek: Differential effects of the site of permanent epicardial pacing on left ventricular synchrony and function in the young: implications for lead placement. Europace (2009) 11, 1654–1659
[3] Janousek J. et Al: Permanent Cardiac Pacing in Children - Choosing the Optimal Pacing Site: A Multi-Center Study. "submitted for publication to Circulation"

Descriptive statistics:

| Parameter | Pacing-site | | | | | | | P | |
|---|---|---|---|---|---|---|---|---|---|
| | RVOT | RVLat | RVA | RVS | LVA | LVLat | LVB | overall | between groups |
| N | 8 | 44 | 61 | 29 | 12 | 17 | 7 | - | - |
| Male/Female [N] | 7\|1 | 21\|23 | 33\|28 | 11\|18 | 1\|11 | 6\|11 | 3\|4 | 0.016 | - |
| CCAVB [N] | 6 | 35 | 47 | 20 | 9 | 16 | 5 | 0.467 | - |
| Maternal ABs [N] yes/no | 5\|3 | 16\|22 | 19\|27 | 12\|13 | 7\|2 | 5\|3 | 0\|2 | 0.26 | - |
| LVEDD preimpl. [z-score] mean (SD) | 1.64(1.06) | 1.81(1.79) | 1.79(1.74) | 2.11(1.96) | 1.71(2.13) | 1.49(0.85) | 1.53(1.98) | 0.980 | - |
| LVSF preimpl. [%] mean (SD) | 42(5) | 38(7) | 41(7) | 43(7) | 40(5) | 42(8) | 41(5) | 0.359 | - |
| LVEF preimpl. [%] mean(SD) | 65(14) | 66(12) | 62(12) | 61(14) | 68(14) | 60(11) | 64(5) | 0.632 | - |
| Age at impl. [years] mean (SD) | 3.52(5.61) | 2.85(3.64) | 5.32(4.29) | 6.76(5.43)[2] | 1.69(2.50)[1] | 3.78(4.61) | 6.34(6.32) | 0.0016 | 0.0002 1 vs 2 |
| Age at follow-up [years] mean (SD) | 7.02(5.38) | 9.73(4.50) | 12.62(4.91)[2] | 12.78(4.36)[2] | 4.08(2.98)[1] | 10.08(5.68) | 11.72(5.17) | <0.0001 | 0.0001 1 vs 2 |
| Duration of pacing [years] mean (SD) | 3.51(1.77) | 6.87(3.85)[2] | 7.31(4.25)[2] | 6.02(4.21) | 2.38(0.97)[1] | 6.30(4.02) | 5.39(3.84) | 0.002 | 0.0001 1 vs 2 |
| DDD pacing at follow-up [N] | 6 | 11 | 33 | 16 | 6 | 10 | 6 | 0.007 | - |
| QRS duration at follow-up [ms] mean (SD) | 143(13) | 157(20)[2] | 157(21)[2] | 146(19) | 127(23)[1] | 158(25) | 177(22)[2] | 0.0001 | 0.0001 1 vs 2 |

*Table 1: Demographic, clinical and pacing parameters according to the ventricular pacing-site*

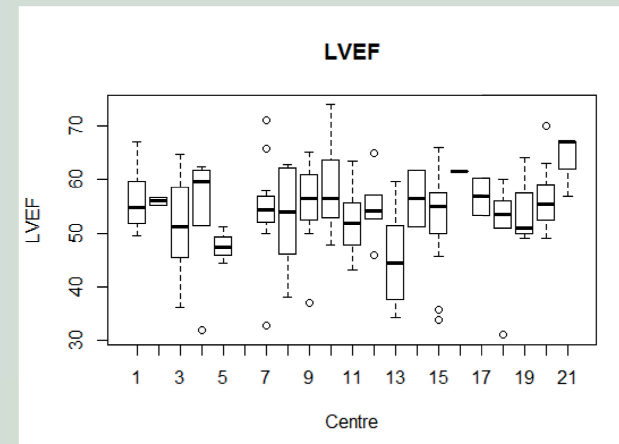


*Figure 1: Box Plot classified by "Centre".*

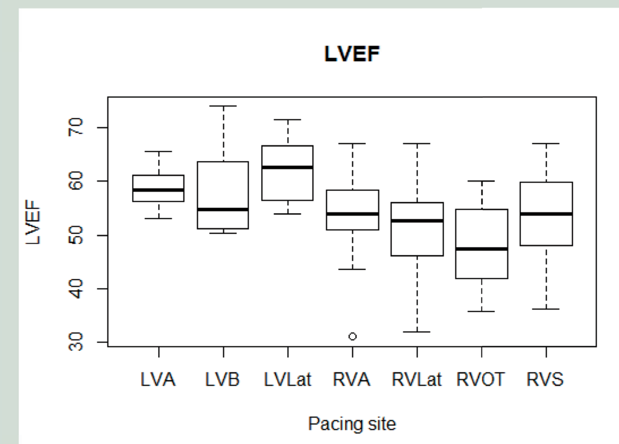


*Figure 2: Box Plot classified by "Pacing site".*

**Analysis of continuous response variable with respect to "Centre".**

| Resp | Effect | NumDF | DenDF | FValue | ProbF |
|---|---|---|---|---|---|
| lv_ef | age_impl | 1 | 104,0 | 0.03 | 0.8564 |
| lv_ef | gender | 1 | 99.9 | 0.64 | 0.4266 |
| lv_ef | pacedur | 1 | 103,0 | 0.14 | 0.7045 |
| lv_ef | QRS_duration | 1 | 103,0 | 0.38 | 0.5415 |
| lv_ef | matantib | 1 | 98.9 | 1.04 | 0.3113 |
| lv_ef | conblock | 1 | 103,0 | 0.36 | 0.5508 |
| lv_ef | DDD_pacing | 1 | 103,0 | 0.02 | 0.9010 |
| lv_ef | site | 6 | 100,0 | 6.23 | <.0001 |

*Table 2: Results of Type I tests*

**Analysis of continuous response variable with respect to "Centre".**

| Resp | Site | Estimate | StdErr |
|---|---|---|---|
| lv_ef | LVA | 60.9785 | 3.1834 |
| lv_ef | LVB | 66.1860 | 5.9990 |
| lv_ef | LVLat | 65.2773 | 2.8971 |
| lv_ef | RVA | 55.4213 | 1.6303 |
| lv_ef | RVLat | 49.8670 | 1.6377 |
| lv_ef | RVOT | 47.7708 | 3.1824 |
| lv_ef | RVS | 54.3964 | 2.0913 |

*Table 3: LSmeans and their standard errors*

**Analysis of continuous response variable with respect to "Centre".**

| Resp | Site | _site | Estimate | StdErr | DF | tValue | Probt | Adjp |
|---|---|---|---|---|---|---|---|---|
| lv_ef | LVA | LVB | -5.2075 | 6.5991 | 103,0 | -0.79 | 0.4319 | 0.9855 |
| lv_ef | LVA | LVLat | -4.2988 | 3.9812 | 103,0 | -1.08 | 0.2828 | 0.9326 |
| lv_ef | LVA | RVA | 5.5572 | 3.4468 | 103,0 | 1.61 | 0.1100 | 0.6748 |
| lv_ef | LVA | RVLat | 11.1115 | 3.4020 | 101,0 | 3.27 | 0.0015 | 0.0243 |
| lv_ef | LVA | RVOT | 13.2077 | 4.2652 | 103,0 | 3.10 | 0.0025 | 0.0394 |
| lv_ef | LVA | RVS | 6.5820 | 3.6243 | 104,0 | 1.82 | 0.0722 | 0.5405 |
| lv_ef | LVB | LVLat | 0.9087 | 6.0590 | 101,0 | 0.15 | 0.8811 | 1.0000 |
| lv_ef | LVB | RVA | 10.7647 | 6.1709 | 99.9 | 1.74 | 0.0842 | 0.5882 |
| lv_ef | LVB | RVLat | 16.3190 | 6.1059 | 102,0 | 2.67 | 0.0088 | 0.1162 |
| lv_ef | LVB | RVOT | 18.4152 | 6.7667 | 103,0 | 2.72 | 0.0076 | 0.1036 |
| lv_ef | LVB | RVS | 11.7895 | 6.3649 | 99.3 | 1.85 | 0.0670 | 0.5165 |
| lv_ef | LVLat | RVA | 9.8560 | 3.2099 | 97,0 | 3.07 | 0.0028 | 0.0424 |
| lv_ef | LVLat | RVLat | 15.4103 | 3.0514 | 104,0 | 5.05 | <.0001 | <.0001 |
| lv_ef | LVLat | RVOT | 17.5065 | 4.1536 | 104,0 | 4.21 | <.0001 | 0.0010 |
| lv_ef | LVLat | RVS | 10.8808 | 3.4775 | 93.7 | 3.13 | 0.0023 | 0.0360 |
| lv_ef | RVA | RVLat | 5.5543 | 2.0581 | 99.2 | 2.70 | 0.0082 | 0.1093 |
| lv_ef | RVA | RVOT | 7.6505 | 3.4008 | 101,0 | 2.25 | 0.0266 | 0.2791 |
| lv_ef | RVA | RVS | 1.0249 | 2.0375 | 97.6 | 0.50 | 0.6161 | 0.9988 |
| lv_ef | RVLat | RVOT | 2.0962 | 3.4108 | 101,0 | 0.61 | 0.5402 | 0.9962 |
| lv_ef | RVLat | RVS | -4.5294 | 2.5311 | 98.7 | -1.79 | 0.0766 | 0.5582 |
| lv_ef | RVOT | RVS | -6.6257 | 3.5818 | 102,0 | -1.85 | 0.0672 | 0.5182 |

*Table 4: Diferences of LSmeans and corresponding p-values*
*Adjusted for multiple comparisons with respect to Tukey-Kramer inequality*

**Figure : A. Mechanical activation pattern in RV free wall pacing showing early peak negative 2D strain reflecting contraction in the basal and mid-ventricular septum (yellow arrow) and late negative strain peak in the LV free wall (red arrow). An extensive septal to lateral mechanical dyssynchrony with a delay of 300 ms is present. B. Left ventricular 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.**

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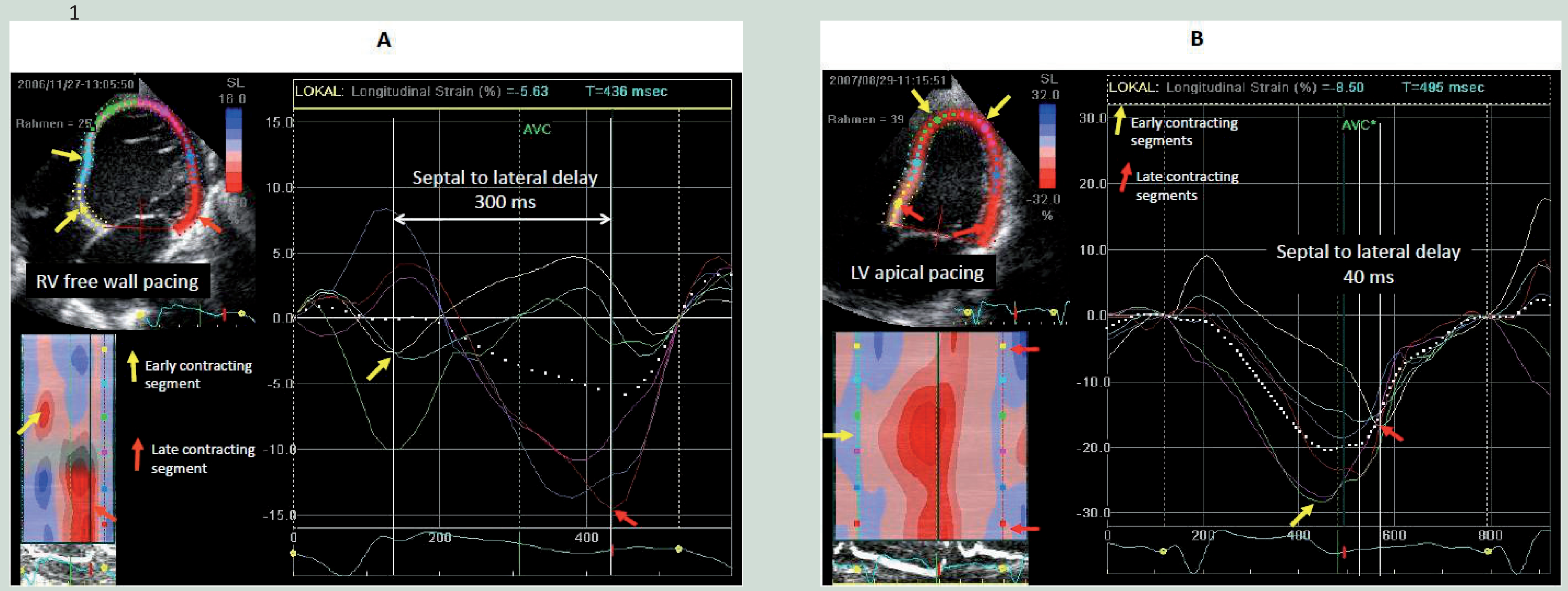


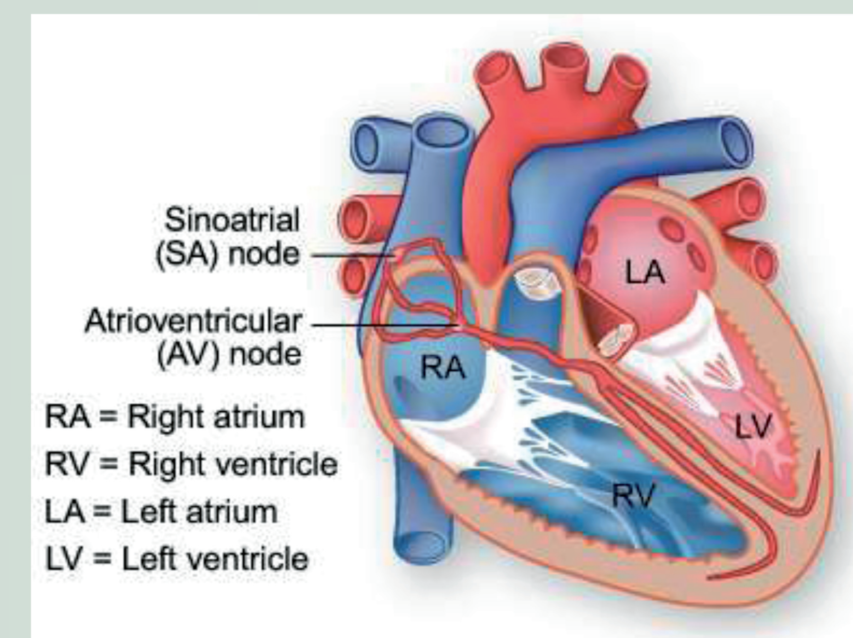


Figure 2: Diagram of the electrical conduction system of the heart [2]

Supported by the grant PřF-2012-017 of the Internal Grant Agency of Palacký University Olomouc.