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Title

Post-operative cardiac implantable electronic devices (CIEDs) in patients undergoing cardiac surgery: a contemporary experience.

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Abbreviations:

AF = atrial fibrillation

AVB = atrioventricular block

AVR = aortic valve replacement

BPM = beats per minute

CABG = coronary artery bypass graft

CIED = cardiac implantable electronic device

ICD = implantable cardioverter defibrillator

LV = left ventricular

PPM = permanent pacemaker

SND = sinus node dysfunction

Abstract

Aims:

Optimum timing of pacemaker implantation following cardiac surgery is a clinical challenge. European & American guidelines recommend observation, to assess recovery of atrioventricular block (AVB) (up to seven days) and sinus node (five days - weeks) after cardiac surgery. This study aims to determine rates of CIED implants post- surgery at a high-volume tertiary centre over three years. Implant timing, patient characteristics and outcomes at 6 months including pacemaker utilization were assessed.

Methods:

All cardiac operations (n=5950) were screened for CIED implantation following surgery, during the same admission, from 2015 - 2018. Data collection included patient, operative and device characteristics; pacing utilization and complications at 6 months.

Results:

250 (4.2%) implants occurred; 232 (3.9%) for bradycardia. Advanced age, infective endocarditis, LV systolic impairment and valve surgery were independent predictors for CIED implants ($p<0.0001$). Relative risk (RR) of CIED implants and proportion of AVB increased with valve numbers operated (single–triple) vs. non-valve surgery: RR 5.4 (95% CI 3.9-7.6) - 21.0 (11.4-38.9) CIEDs.

Follow-up pacing utilization data were available in 91%. Significant utilization occurred in 82% and underutilization (<1% A and V paced) in 18%. There were no significant differences comparing utilization rates in early (≤day 5 postoperatively) vs. late implants ($p=0.55$).

Conclusions:

Multi-valve surgery has a particularly high incidence of CIED implants (14.9% double, 25.6% triple valve). Age, LV systolic impairment, endocarditis and valve surgery were

independent predictors of CIED implants. Device underutilization was infrequent and uninfluenced by implant timing. Early implantation should be considered in AVB post multi-valve surgery.

Key words: Cardiac surgery, pacemaker implantation, atrioventricular block

Introduction

The management of brady-arrhythmia following cardiac surgery is a clinical challenge. Optimum timing for device implantation must balance patient safety, prolonged hospitalization and future pacemaker under-utilization following rhythm recovery. Patients requiring permanent pacemaker (PPM) implantation following cardiac surgery are a heterogeneous group and European Society of Cardiology guidelines recommend prolonged observation for "up to 7 days" in high degree atrioventricular block (AVB) or "5 days to weeks" in sinus node dysfunction (SND). The 2018 ACC/AHA/HRS guidelines categorize recommendations by surgical operative type and recognize the need to individualize patient care. Waiting periods suggested for rhythm recovery include: 3 – 5 days for tricuspid and aortic valve surgery, 5-7 days in mitral valve and CABG.(2)

Post-operative high degree AVB is an important diagnosis with increased morbidity and mortality (3). Risk markers identified in some cohorts for persistent AVB include advanced age, LV systolic dysfunction, prior cardiac surgery (4), infective endocarditis (5), aortic valve surgery (5), cold blood cardioplegia (6), cardiopulmonary bypass and aortic cross-clamp time (7).

The development of new fascicular block following CABG with cardiopulmonary bypass (CPB) is common, occurring in approximately 22-23%.(7) Studies of PPM implantation rates across all types of cardiac surgery demonstrate rates of 1.4-6.7%, with incidence of all CIEDs ranging between 0.4–9.7%.(7-11) The Cleveland Clinic published the largest single centre cohort, demonstrating a 4.1% incidence of postoperative CIED implant.(4)

Persistent complete AVB has been suggested as an important predictor of dependency at follow-up.(12-13) A systematic review (10 studies with 780 patients receiving PPMs post cardiac surgery) demonstrated pacemaker dependency rates of 32-91% and AV conduction recovery in 16-42%.(13)

Most published cohorts describing CIED implantation following cardiac surgery involve long historical cohorts with predictors of rhythm recovery and pacing dependence being ill defined.

In this study, we aimed to assess the incidence and characteristics of patients undergoing cardiac surgery, requiring postoperative CIED implantation during the same admission; evaluated over a contemporary 3-year period in a large tertiary referral cardiac centre.

We hypothesized that increasing number of valves operated on would be the strongest predictor of CIED implantation following cardiac surgery. Additionally, early PPM implantation for persistent AV block would be justified and would not lead to a significant increase in device under-utilization at follow-up.

Methods

Study Population and Data Sources:

This study is a retrospective, single centre, cohort study exploring "real world" CIED implantation practice following cardiac surgery. The National Institute for Cardiovascular Outcomes Research database was cross-referenced with our institutional data. The study was approved by the clinical effectiveness department at Barts Health NHS Trust.

All patients undergoing cardiac surgery of any type were included. This involved 21 operating surgical consultants across the search period. Trans-catheter Aortic Valve Implantation (TAVI) procedures were excluded. The search strategy identified patients with CIED implantation during the same admission, following surgery over 3 years (April 2015 - May 2018). The following exclusions were applied:

1. Patients with pre-operative indications for CIED implantation.
2. Patients with pre-existing CIEDs requiring post-operative intervention e.g. lead repositioning or replacement.
3. Device implants occurring during a separate admission to the index surgical procedure.

Electronic patient records and our institutional database (Mediconnect®) were used to collect patient and device related data. District general hospitals were contacted to obtain missing follow-up information for patients with follow-up transferred to other centres. Collection of patient demographics and baseline characteristics including the following: pre-operative cardiac rhythm, operative details, device indication, procedural details and co-morbidities.

<u>Study outcomes:</u>

The primary study outcome was CIED implantation following cardiac surgery. Secondary outcomes included PPM under-utilization and dependence, as defined below.

<u>Device Utilization:</u>

Follow-up device interrogation data were analysed at six months post implantation. Underlying rhythm and % of pacing support were reviewed. No standardized definitions exist within the literature however we defined significant pacemaker utilization as any of the following being present:

1. Underlying rhythm with ventricular rate of less than 40 beats per minute (bpm).
2. Persistent high degree AV (second- or third-degree AV block).
3. Greater than 1% atrial or ventricular pacing.

If all these criteria were absent, then underutilization status was allocated. Pacing dependence was defined as underlying rhythm <40 bpm or ventricular pacing >60%.

Assessment of underlying rhythm was performed by a standard method involving gradual reduction of the programmed base rate in increments of 10 bpm to 30 bpm as tolerated.

Patient characteristic and demographic data are presented as number (%) for categorical variables and mean (± standard deviation) for continuous variables. Univariate analyses were performed using 2 tailed p values, Fisher's exact test for categorical variables and unpaired t-test for continuous variable. Multivariate analyses were performed using a logistic regression model (IBM SPSS Statistics v25). Missing data was imputed by multiple imputation by chained equations and the pooled result is presented. A complete case analysis was also run as a sensitivity analysis to assess bias. Confidence intervals of 95% were used with p values of <0.05 considered statistically significant. Statistical support was provided by Ms J Cooper MSc (Queen Mary University of London).

Results

5950 patients underwent cardiac surgery during the search period with 262 CIED postoperative implanted during the same admission. 12 post-surgical implants were excluded. The overall rate of CIED implantation post-operatively was 4.2%, 250 implants. 3.9%, 234 implants occurred for bradycardia indications. 12 (0.2%) Implantable Cardioverter Defibrillators (ICDs) implants occurred for secondary prevention and 4 (1.6%) for primary prevention without bradycardia indications. Devices implanted included: 39 (15.6%) single chamber PPM, 161 (64.4%) dual chamber PPM, 6 (2.4%) single chamber ICD, 12 (4.8%) dual chamber ICD, 16 (6.4%) CRT-D, 16 (6.4%) CRT-P.

Exclusions:

12 implants were excluded: 6 abdominal epicardial pacemaker generator changes, 2 planned surgical PPM implants with epicardial leads and 2 pre-existing pacemakers requiring

lead revision following cardiac surgery; 1 pre-existing PPM upgraded to a defibrillator for secondary prevention and 1 PPM generator change.

Baseline characteristics:

Table 1 displays demographics and baseline characteristics of the non-CIED implant surgical cohort and the CIED implant cohort. Of the 250 patients with CIED implants, 68 (27.2%) were female. Mean (SD) age 67.6 (± 13.5), range 23 – 95 years, and Euroscore II 5.7 (± 6.4). Twenty-six (10.4%) patients had re-do cardiac surgery and 20 (8.0%) operations were for infective endocarditis. Re-do surgery and endocarditis were both significantly higher proportions of the CIED group than the whole surgical cohort ($p<0.0001$).

The CIED implant group was also significantly older ($p<0.0001$) and the baseline LV EF was significantly different in the CIED implant group with a higher proportion of LV systolic impairment of all categories. Baseline characteristics and operative urgency were otherwise similarly matched between the CIED implants and the whole surgical cohort.

Pre-operative Rhythm and Implant Indication

Documented pre-operative rhythm abnormalities were present in the following: fascicular disease, 5 (2.0%), atrial fibrillation (AF) / flutter, 54 (21.6%). Figure 1 displays the CIED indication by rhythm diagnosis, these included: third degree AV block in 164 (65.6%) patients, second degree AV block in 15 (6.0%), SND in 30 (12.0%), AF / flutter with slow ventricular rate in 14 (5.6%), trifascicular block (1^{st} degree AV block with bifascicular block) in 7 (2.8%), asystole in 4 (1.6%), 14 (5.6%) secondary prevention ICDs, 4 (1.6%) primary prevention ICDs. The diagnosis of asystole was assigned to patients with no underlying rhythm present at the decision for CIED implant, sinus arrest with no ventricular escape.

Of the patients with AF / flutter and slow ventricular rate, 3/14 were receiving rate limiting drugs prior to CIED implant (1 x amiodarone, 2 x beta-blocker). 7/14 (50%) of these patients had previously documented high degree block which had become intermittent or resolved. The remaining patients had AF / flutter with slow ventricular rate despite absence of rate limiting drugs.

Operative Details:

The number of operations and CIED implants by operative type are displayed in Table 2. Comparison between non-valve surgery and increasing number of valves operated on is included with relative risk of CIED implant. There is a significant increase in relative risk of CIED implant with increasing number of valves operated on, with single, double and triple valve surgery having a 5.4 (95% CI 3.9-7.6),12.2 (95% CI 8.2-18.2) and 21.0 (95% CI 11.4-38.9) relative risk of CIED implant respectively, all with p value of < 0.0001.

Data for the mean cumulative cardiopulmonary bypass (CPB) times and aortic cross clamp (XC) times are shown in table 1. Mean (±SD) CPB time (minutes) was 110.7 (± 56.0) for the non-CIED implant surgical cohort and 131.9 (± 60.6) for the CIED implant cohort. Mean aortic XC time (minutes) of 78.0 (±39.5) for the non-CIED implant surgical cohort and 96.7 (±48.5) for the CIED implant cohort. The CPB and cross clamp times were significantly longer in the CIED implant cohort (p<0.001).

Multivariate Analysis of CIED Implant Predictors

Multivariate analysis was performed with CIED implant status as the dependent variable. Independent variables used in the model included: patient age at time of surgery, gender, diabetes mellitus, chronic kidney disease (dialysis or eGFR >200mmol/L pre-operatively), LV ejection fraction, presence of coronary artery disease (single, double or triple vessel), active endocarditis, previous cardiac surgery, cardiopulmonary bypass cumulative time, aortic cross clamp cumulative time and number of valves operated. Variables found to be independent predictors of CIED implant status included the following: patient age, impaired LV EF, active endocarditis and increasing number of valves operated. Table 6 displays the odds ratios, 95% confidence intervals lower and upper limits and p values for each variable. The odds ratios increase incrementally with severity of LV EF reduction and the number of valves operated.

Timing of CIED Implants:

Figure 2 demonstrates the distribution of CIED implants by day of implant following cardiac surgery. Median day of device implant post-surgery was 7.0 days (± 6, range 0 - 45). Median day of hospital discharge post device implant was 5 days (± 16, range 0 - 104). Median length of inpatient hospital stay was 14 days (± 18, range 5 - 146). Fifty-six (22.4%) patients were discharged within 2 days of device implant.

Sixty-six (26.4%) devices were implanted early at ≤ 5 days post-surgery, 184 (73.6%) devices were implanted late at > 5 days post-surgery. The early device implant group had a higher proportion of high degree AV block indications with 80% (53/66) vs 68% (126/167) in the late implant group although this difference was non-significant ($p = 0.4931$). A comparison of the waiting period for device implants between implants with indications of high degree AV block (median 8.5 days, SD 5.5) vs. non-AV block (median 9.8 days, SD 7.1) also demonstrated no significant difference ($p = 0.1308$, CI -3.00 to 0.39).

Follow-up and Complications:

6-month follow-up data were available in 233 (93%) patients. Complications occurred in 13 (5.2%). These included 5 (2.0%) lead displacements requiring repositioning, 2 (0.8%) leads with increased pacing thresholds requiring revision, 2 (0.8%) pocket infections requiring system explant, 4 (1.6%) minor pocket hematomas managed conservatively. Complication rates were comparable to our institution's audit data for the whole of 2018 which has shown infection rates of 0.75%, lead displacement 2.4%, haematoma 0.67%. Mortality: 7 (2.8%) patients were deceased within 30 days of CIED implants post-surgery, this is comparable to an institutional 30-day mortality rate of 2.9% for the whole surgical cohort.

161 patients were receiving anticoagulation therapy following cardiac surgery; 124, warfarin, 28 Direct oral anticoagulants (DOACs) and low molecular weight heparin/heparin in 8 patients. There was no significant difference ($p = 1.0$) in bleeding complications comparing patients receiving anticoagulants (3/161, 1.9%) vs. no anticoagulant (1/89, 1.1%).

Pacing Utilization:

Primary and secondary prevention ICDs without bradycardia indications were excluded from pacing utilization data. Table 3 displays pacing utilization data by operative type at follow-up. 6-month utilization data were available in 203 (86.8%) of 234 implants with bradycardia indications. 166 (81.8%) had significant utilization, 37 (18.2%) were underutilized and 93 (46%) were pacing dependent. There was a trend towards reduced device underutilization at follow-up with increasing number of valves operated on. Double and triple valve surgery had the lowest rates of underutilization at 5.4% and 0% respectively.

A comparison of device utilization at follow-up in devices implanted early (≤ 5 days postoperative) vs. late (>5 days) is displayed in table 4. The proportion of pacing dependence at follow-up was significantly higher in early implants: 34/59 (57.6%) vs. 59/144 (41.0%) in late implants ($p = 0.0433$). The proportion of underutilized devices at follow-up was not significantly different in late implants 27/144 (18.8%) vs. 10/59 (16.9%) early implants ($p=0.8432$).

A comparison of the characteristics of patients with underutilized devices and those with pacing dependence at 6 months follow up is displayed in table 5. There was a statistically significant difference in the proportion of AV block as indication for device implant with 85% in the pacing dependent vs. 65% in the under-utilized group ($p=0.016$). Additionally, fewer urgent or emergency operations occurred in patients with underutilized devices although the difference was non-significant. In addition, there were fewer complex valve operations (double and triple valve) in the underutilization group. Non-valve and single valve operations made up the majority of all underutilized devices (89.2%, 33/37).

Discussion

This study provides a contemporary, large cohort of post-cardiac surgical patients requiring CIED implantation including 6 months pacing utilization follow up data. The incidence of post-surgical CIED implantation at our centre was 4.2% for all CIEDs, 3.9% for bradycardia indications, in keeping with published historical data. Isolated CABG carries the lowest risk of CIED implant; 1.2% for all indications and 0.9% for bradycardia. An incremental increase in the risk of CIED implant is seen with increasing number of valves operated on and complexity. Double and triple valve surgery carry significantly higher incidences and relative risks of CIED implant: RR 12.2 and 21.0 respectively, compared to non-valve surgery. Multivariate analysis revealed clinical predictors for CIED implantation in this cohort include advanced age, LV systolic impairment, active infective endocarditis and valve surgery. Odds of CIED implantation increased incrementally with increasing number of valves operated and greater severity of LV EF impairment. The CIED implant cohort also had significantly longer cumulative CPB times and aortic cross clamp times although non-significant on multivariate analysis.

Within valve sub-types, surgery involving the tricuspid, then the mitral valve conveys the highest risk. It is noteworthy that tricuspid valve surgery was rarely performed in isolation and predominantly performed as part of multi-valve surgery. Only 19 isolated tricuspid valve operations were performed within the search period, with two of these patients receiving postoperative PPMs (10.5%). It is also noteworthy that the aortic valve replacement subgroup (n = 132) had a 6.0% incidence of PPMs for bradyarrhythmia. This is of particular relevance when comparing trans-catheter vs surgical aortic valve replacement.

The incremental increase in incidence of CIED with increasing number of valves clearly demonstrated by our study was also suggested by retrospective data spanning 14 years and 135,356 cardiac operations from a United Kingdom national database.(14) This showed that multi-valve surgery, male gender, emergency admission, pre-existing diabetes mellitus, heart failure, and renal impairment were all independent predictors of PPM implantation. This study also demonstrated a persistent, long-term risk of requiring PPM following valve surgery. Our study highlights that the true rates are higher than those found from this nationwide registry which showed post-operative rates of 5.6% & 7.9% compared to our rates of 14.6% & 23.1% for double and triple valve surgery respectively. This difference may be explained primarily by the higher sensitivity of our data search strategy with the ability to cross reference and verify individual patient records from local data.

The mechanism by which increasing number of valves operated on adds incremental risk of device implant and high degree AV block is likely to be multifactorial. Direct trauma to the heart's conduction tissue and proximity of the surgical site to the AV node and Bundle of His are likely to be the main factors. These operations are more likely to be of longer duration with longer cross clamp and cardiopulmonary bypass times, supported by the differences in these times between CIED and non-CIED cohorts in this study. Whether prolonged CPB / cross clamp times are causative or associated with bradyarrhthmias is unclear from this study.

Additionally, patients requiring multi-valve surgery are also more likely to have medical co-morbidities, advanced age, LV systolic impairment, infective endocarditis and have had previous cardiac surgery; all of which are recognized risk markers for postoperative AV block and PPM implant.

This study gives an accurate representation of device utilization and complications (5.6%) which were low at 6-month follow-up. Device underutilization rates (18.2%) at follow up were in keeping with published historical data.(13) Post-operative anticoagulant use did not influence complication rates. Although these data do not describe the precise timing of anticoagulant initiation relative to CIED implant, the outcomes are in keeping with the Bruise Control & Control-2 trial results demonstrating the safety of uninterrupted warfarin and DOAC use in the peri-procedural phase. (15,16)

Those with an indication of high degree AV block were implanted significantly earlier. High degree AV block also has the highest rate of pacing dependence and lowest rate of underutilization at follow-up compared to other indications. Increasing number of valves operated was associated with a lower rate of device underutilization at follow-up however pacing dependence rates were similar across all surgical operative types. Comparing implant timing does not predict device utilization and importantly early implants did not have increased rates of underutilization.

Definitions of device utilization are heterogeneous within the literature as displayed by a recent systematic review comparing pacemaker dependency rates.(13) The definition of pacemaker dependence is particularly variable and highly influenced by pacemaker programming. In order to have a truly robust pacemaker dependence assessment, both programming and interrogation technique need to be considered. For this reason, the definition we have used for underutilization (<1% A and V paced) is intentionally strict and our pacing dependence data should be interpreted with caution.

Our findings support earlier post-operative device implantation in general, specifically in patients with persistent high degree AV block following multi-valve surgery. In this group zero % of triple and only 6.4% of patients undergoing double valve surgery underutilized their pacing devices; this cohort could justifiably be implanted early (≤5 days post-operatively). This could lead to reduced length of hospitalization with gains for both patient experience and admission cost. Non-valve and single valve surgery have marginally higher rates of underutilized devices at follow up. There were no other specific clinical indicators identified that predicted late recovery of intrinsic rhythm leading to pacing underutilization at follow up.

This single-centre study with large numbers of patients receiving CIED implants (250) over a 3-year period significantly exceeds previous studies over similar timescales (20-151 patients per study).(17-19) Studies with device utilization follow-up data also tend to be small in size, illustrated by a recent systematic review, which identified eight studies with follow-up utilization data available in 609 of 728 patients, 83.7% compared to this study with follow-up utilization data in 87.6%.(13) The only study including device utilization follow-up data with higher patient numbers (326 patients with post-operative PPM for high degree AVB) spanned 15 years of cardiac surgery.(20)

Study Limitations

There are several limitations to this study, however its strengths include the contemporary nature of the data and the cohort size. The search strategy has provided an accurate assessment of CIED implant incidence, it has not however included patients who avoided device implantation during a period of observation post-operatively. Nor has it defined the waiting periods with post-operative bradycardia who avoided PPM implantation. This would require a prospective approach to inclusively record evolution of post-operative cardiac rhythm to establish timing of recovery and predictive factors. We have also not been able to comprehensively assess baseline 12 lead electrocardiograms in all patients and cannot draw meaningful conclusions regarding pre-existing conduction disease and risk factors for PPM implantation. Another limitation of this dataset is the lack of full details regarding antiarrhythmic or AV nodal blocking drug use for all patients. Due to the retrospective nature of this study, the accurate timing and dose administration of drugs was not available in all patients for comparison.

Device underutilization was used as a surrogate for rhythm recovery at follow-up. There are however several factors other than the underlying rhythm that can alter the burden of pacing delivered, mainly device programming which we have not assessed in this study. Pacing utilization of <1% A and V pacing was considered significant for device underutilization however it is only a surrogate for rhythm recovery and should not be interpreted as this. It is still possible that a PPM could justifiably be required on a symptomatic and prognostic basis <1% of the time for infrequent, important bradycardia. It is also possible that this will miss patients with rhythm recovery but >1% pacing due to device programming.

Conclusions

The incidence of postoperative CIED implants in this study was in keeping with published historical data, 4.2% for all CIEDs and 3.9% for bradycardia indications. Clinical indicators associated with implants included advanced age, LV systolic impairment, valve surgery and infective endocarditis. Multi-valve surgery was the strongest predictor for CIED implantation and risk incrementally increased from double to triple valve surgery. The high rates of PPM following multi-valve surgery have important implications for the surgical consent process pre-operatively. These results suggest that early device implantation should be considered, particularly in high degree AV block following multi-valve surgery. This hypothesis will need to be verified in a prospective study.

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