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# Predictors of hemodynamic compromise with propofol during defibrillator implantation: a single center experience

**Khyati Pandya · Mehul B. Patel · Jaya Natla · Abhijeet Dhoble · Terry Habetler · Jeffrey Holliday · Renee Janes · Sujeeth R. Punnam · Joseph C. Gardiner · Ranjan K. Thakur**

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**Abstract**
*Background* Intra-operative hypotension has been reported in cardiac resynchronization therapy defibrillator (CRT-D) clinical trials but this phenomenon is not well characterized. The purpose of this study was to understand the frequency and determinants of intra-operative hypotension in patients undergoing defibrillator implantations.
*Methods* We retrospectively reviewed clinical data of all CRT-D implantations over a 21-month period. We compared a randomly selected contemporaneous group undergoing implantable cardiac defibrillator (ICD) implantations as a reference group. Procedure protocol involved intra-arterial blood pressure monitoring throughout the case. Lidocaine (1%) was routinely used along with propofol for sedation in all patients. Procedure time was defined as the time from initial administration of lidocaine for arterial line access, to completion of defibrillator pocket closure. Cumulative dose of propofol was calculated in each patient. Hypotension was defined as a fall in the systolic blood pressure of ≥30% from baseline or a systolic blood pressure of ≤80 mm Hg for >3 min. CRT-D and ICD patients were divided into hypotensive and non-hypotensive subsets.
*Results* The incidence of hypotension in the CRT-D group ($N$=100) was 56%, as compared to 40% in the ICD group ($N$=97). The mean duration of procedure in the CRT-D group was 114±95 min in the hypotensive subset versus 69±31.9 min in the non-hypotensive subset ($p$=0.0015). The mean NYHA class in the hypotensive subset of the CRT-D group was 2.85±1.2 vs 2.2±1.5 in the non-hypotensive subset ($p$=0.0179). Cumulative dose of propofol in the hypotensive subset of the CRT-D group was 386±22 mg, while that in the non hypotensive subset was 238.3±17 mg ($p$<0.0001). Creatinine clearance in the hypotensive subset of the CRT-D group was 63.8±12.8 ml/min, while that in the non-hypotensive subset was 78.7±23.5 ml/min ($p$=0.003). Patients in the CRT-D group who developed hypotension had a lower left ventricular ejection fraction of 21.1±10.2% versus 29±14.8% in the non-hypotensive subset ($p$=0.0035).
*Conclusions* Hypotension is a common occurrence during defibrillator implantation under conscious sedation. Risk factors for significant hypotension include: higher NYHA class, lower left ventricular ejection fraction, lower creatinine clearance, higher doses of propofol and longer procedure times.

**Keywords** Propofol · Procedure time · ICD · CRT-D · Complications

K. Pandya · M. B. Patel · J. Natla · A. Dhoble · T. Habetler · J. Holliday · R. Janes · S. R. Punnam · R. K. Thakur (✉)
Thoracic and Cardiovascular Institute, Sparrow Health System,
Michigan State University,
405 West Greenlawn, Suite 400,
Lansing, MI 48910, USA
e-mail: thakur@msu.edu

J. C. Gardiner
Department of Epidemiology and Biostatistics,
Michigan State University,
Lansing, MI, USA

## 1 Introduction

Availability of cardiac resynchronization therapy (CRT-D) implantable cardiac defibrillator (ICD) for patients with refractory congestive heart failure (CHF) has been a significant addition in the therapeutic armamentarium. Patients undergoing CRT-D implantation have low ejection fractions (EF), poor cardiac reserve, advanced heart failure and are generally on several medications that may interfere

with a physiologic response to hemodynamic compromise. The incidence of procedure related complications and deaths associated with implantation of CRT-D devices in clinical trials have been reported to be 20% and 0.4% respectively [1]. Several large randomized CRT-D trials have reported peri-procedural deaths related to hypotension and asystole [2–4]. However, the predictors of hypotension have not been adequately studied.

Propofol is widely used for conscious sedation for electrophysiologic procedures in the catheterization laboratory (device implantations, ablation procedures, cardioversions, etc.). One of the major undesirable effects of propofol includes cardiovascular depression [5]. We have previously reported a case series of patients who experienced hemodynamic collapse during CRT-D implantation [6]. The purpose of the present study was to determine the frequency and predictors of intra-operative hypotension in patients undergoing CRT-D implantations.

## 2 Methods

### 2.1 Patient population and study design

This is a single center retrospective study in which 100 consecutive patients undergoing CRT-D implantation and a reference group of 97 patients undergoing ICD implantation were compared. The analysis was approved by the institutional review board. All CRT-D implantations over a 21-month period from January 2005 to September 2006 were reviewed. We compared a random sample from a contemporaneous group over the same time period undergoing ICD implantations as a reference group. We used our cardiac catheterization laboratory database and electronic patient records for the study.

Due to the short procedure time for pulse generator change, patients undergoing isolated generator change were excluded. Implantations of ICDs for both primary and secondary prevention were included in the analysis.

### 2.2 Patient preparation

Patients undergoing implantation were in the post-absorptive state for at least 8 h. The cardiac catheterization laboratory was equipped with complete anesthesia infrastructure along with two external defibrillators. The laboratory was staffed by two cardiac technicians, two advanced life support trained nurses, and an attending anesthesiologist. Oxygen saturation was monitored by pulse oximeter, and all patients received supplemental oxygen either by a mask or nasal canula. All patients had intra-arterial blood pressure monitoring throughout the procedure. Patients were closely monitored by trained nursing staff and procedural details were recorded continuously in an electronic chart. After completion of the procedure, patients were observed in the laboratory until awake, prior to transferring to the post-anesthesia observation area. Hypotension was initially treated with intravenous infusion of normal saline. If systemic pressures failed to rise, intravenous phenylephrine infusion was administered at the discretion of the anesthesiologist. This was further supplemented with either intravenous dopamine or norepinephrine, if needed in case of failure of response to fluid administration and phenylephrine.

### 2.3 Conscious sedation

"Conscious sedation" was defined as a moderate level of sedation such that the patient maintained his/her own airway with or without the use of an oral or nasal airway during the procedure. It was achieved with a combination of propofol with either midazolam or fentanyl in all patients and was monitored by an anesthesiologist. These drugs were administered intravenously from the start of the procedure. The standard dose of medications administered was 0.05 to 0.1 mg/kg/min of propofol along with either 2 to 4 mg of midazolam or 50 micrograms of fentanyl. Incremental doses of all agents were titrated during the procedure to ensure adequate sedation and patient comfort. Blood pressure was continuously monitored, but charted in the electronic record at 3-minute intervals. Additional measurements were obtained within 1– 2 min of administering propofol. The cumulative dose of all sedatives was calculated individually. Local anesthesia at the implant site was achieved using 1% lidocaine without epinephrine. The total volume of local anesthetic ranged between 10 to 30 ml.

### 2.4 Implantation technique

All implantations (CRT-D and ICD) were performed in the infra-clavicular region. Venous access of the axillary vein was achieved under fluoroscopy using the Seldinger technique. A subcutaneous pocket was fashioned over the pectoralis major muscle using an electrocautery pen. All leads were positioned in their respective chambers. After obtaining adequate pacing and sensing parameters, the leads were secured to the pectoralis fascia and connected to the generator. The pulse generator was then placed in the pocket. Defibrillation threshold testing was performed by inducing at least 2 episodes of ventricular fibrillation. The pocket was then irrigated with antibiotic solution and closed in layers.

### 2.5 Data collection

Baseline demographics such as age, gender, underlying rhythm, cardiac function, and renal function were recorded.

Indication for CRT-D and ICD included patients with ischemic or non-ischemic cardiomyopathy. The total procedure time was defined as the time from initial administration of lidocaine for arterial line access, to completion of skin closure. The total dose of anesthetic and sedative agents given throughout the procedure was calculated. Hypotension was defined as a fall in the systolic blood pressure (SBP) of ≥30 % from baseline or a SBP of ≤80 mmHg for >3 min. CRT-D and ICD groups were divided into hypotensive and non-hypotensive subsets. Patients receiving ICD implantation served as the reference group.

### 2.6 Statistical analysis

Analysis was performed with the Statistical Package for Social Sciences (SPSS version 16, SPSS Inc, Chicago, IL). Descriptive statistics were computed as mean and standard deviation for continuous variables, and as frequencies for categorical variables. Comparisons of baseline patient characteristics were performed using the Student's *t*-test for unequal variance for p values and the $\chi^2$ test for categorical variables. A p-value < 0.05 was considered statistically significant. Ordinal regression analysis on all patients was performed with 'development of hypotension' as a dependent variable to see the effect of an individual variable. General linear model multivariate analysis was used to control for other factors for both ICD and CRT-D groups, while examining for a significant relationship of each individual factor in the development of hypotension. Linear regression analysis was used to examine the relationship between propofol dose and length of procedure in the development of hypotension.

## 3 Results

The cohort comprised 100 patients who underwent CRT-D implantation (CRT-D group) and 97 patients who underwent ICD implantation (ICD group). The groups were further subdivided into hypotensive and non-hypotensive subsets. Hypotension was seen in 56% of patients in the CRT-D group, as compared to 40% in the ICD group ($p$=.038). Clinical data for both groups are summarized in Table 1.

Current ACC/AHA class I indications for CRT-D implantation (NYHA III or IV) were followed. However, several patients underwent CRT-D implantation as part of other heart failure studies, resulting in a mean NYHA class below 3 (2.56+1.3) in the CRT-D group. The mean QRS duration and the initial blood pressure were similar in the hypotensive and non-hypotensive subsets of ICD and CRT-D groups.

There was significant direct correlation between ejection fraction (EF) and New York Heart Association (NYHA) class with development of hypotension in the CRT-D group (p=0.0035 and 0.0179 respectively). Variables that were

**Table 1** Predictors of hypotension in ICD and CRT-D groups

| | ICD (N=97) | | | CRT-D (N=100) | | |
|---|---|---|---|---|---|---|
| | Hypo | Non Hypo | *p*-value | Hypo | Non Hypo | *p*-value |
| N | 40 | 57 | | 56 | 44 | |
| Age (years) | 68.2±12.3 | 69±18.3 | 0.8103 | 70.9±10.5 | 68.6±20.3 | 0.4654 |
| % Males | 76 | 75 | 0.961 | 64 | 77 | 0.159 |
| EF (%) | 26.1±2.5 | 28.5±19 | 0.4298 | 21.1±10.2 | 29±14.8 | **0.0021** |
| % ICM | 78 | 74 | 0.964 | 84 | 86 | 0.734 |
| NYHA | 2.25±1.2 | 2.1±1.1 | 0.5258 | 2.85±1.2 | 2.2±1.5 | **0.0179** |
| CrCl (ml/min) | 64±10 | 70±12.3 | **0.0124** | 63.8±12.8 | 78.7±23.5 | **0.0001** |
| QRS duration (ms) | 99.23+18.45 | 103.52+11.37 | 0.160 | 142.45+22.49 | 137.34+17.55 | 0.218 |
| Initial BP (mm Hg) | 114/61+28/14 | 121/55+31/17 | 0.31 | 118/63+26/18 | 127/59+28 /13 | 0.15 |
| Propofol dose (mg) | 228±23 | 203±22 | **0.0001** | 386±22 | 238.3±17 | **0.0001** |
| Procedure time (min) | 61.65±32.3 | 58.71±33.7 | 0.6684 | 114±95 | 69±31.9 | **0.0033** |
| Mean number of VF episodes | 2.24±0.56 | 2.26±.75 | 0.886 | 2.33±.64 | 2.29±.60 | 0.750 |
| BB+ACEI/ARB | 11 | 18 | | 15 | 13 | |
| ACEI | 7 | 11 | | 11 | 6 | |
| ARB | 5 | 5 | | 9 | 10 | |
| ACEI+ARB | 8 | 11 | | 7 | 6 | |
| BB+ACEI+ARB | 9 | 12 | | 14 | 9 | |

ACEI=ACE inhibitor, ARB=aldosterone receptor blocker, BB=beta blocker, BP=blood pressure), CrCl=creatinine clearance, EF=ejection fraction, ICM=ischemic cardiomyopathy

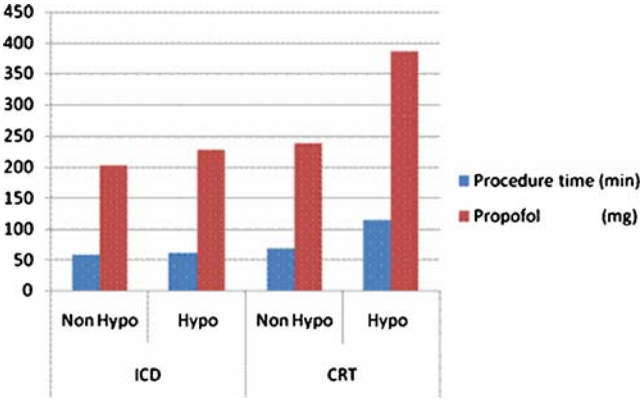


**Fig. 1** Procedure times and cumulative dose of propofol is shown for hypotensive and non-hypotensive subsets of ICD and CRT-D groups

associated with hypotension in both groups included creatinine clearance, propofol dose and procedure time.

Cumulative dose of propofol in the non-hypotensive subset of the CRT-D group was 238.3±17 mg as compared to 386±22 mg in the hypotensive subset ($p<0.0001$). Cumulative dose of propofol in the hypotensive subset of the ICD group was 228±23 mg versus 203±22 mg in the non-hypotensive subset ($p<0.001$). Patients undergoing ICD implantation received a significantly lower dose of propofol compared to those undergoing CRT-D implantation, owing to a significantly shorter duration of procedures (Fig. 1).

The mean procedure time in the hypotensive subsets of both groups was significantly higher than the non-hypotensive subsets. The mean creatinine clearance was significantly lower in the hypotensive subsets of both groups than the non hypotensive subsets. The distribution of ACE-I, ARBs, beta-blockers and combination medications was comparable in all the subsets. None of the medications were discontinued preoperatively as it formed an essential component of heart failure management.

### 3.1 Timing of hypotension

Hypotension was commonly noticed during induction with propofol, except in 18 patients. Two patients developed hypotension during coronary sinus cannulation, and two patients experienced transient hypotension during left ventricular pacing. Extremely short lasting hypotension, not requiring any therapy was seen immediately after VF testing in 12 patients due to unsuccessful internal shocks requiring an external rescue shock. Systolic pressure recovered after 65±32 s enabling a second VF induction and termination. Two patients developed severe prolonged hypotension requiring pressor doses of dopamine, preventing DFT assessment on the same day. These patients required prolonged intravenous dopamine infusion with close monitoring in the intensive care unit. None of the patients developed shock or required IABP support. No patient developed complication secondary to vasoactive drug therapy.

### 3.2 DFT testing

Two patients developed prolonged hypotension requiring dopamine infusion preventing DFT testing on the same day. All remaining patients underwent DFT testing before pocket closure.

Ordinal regression analysis for both groups showed the strongest variable related to the development of hypotension were cumulative dose of propofol, followed by procedure time. However, procedure time was the only independent predictor ($p=0.032$). We further tried to examine the correlation between propofol dose and procedure time using linear regression analysis and found that there was a significant parallel relationship between the two ($p<0.0001$).

### 3.3 Management of hypotension

Hypotension was managed by the attending anesthesiologists on an individual basis depending on the left ventricular ejection fraction (LVEF). For Patients with an LVEF of more than 25%, intravenous saline formed first line therapy, whereas, vasopressors formed first line therapy for patients with an LVEF of <25%.

Treatment for hypotension is shown in Table 2. Thirty patients (75%) in the ICD group received infusion of normal saline while 57% of the CRT-D patients received saline infusion ($p=0.07$). The remainder of patients in either group received vasopressors.

## 4 Discussion

Implantation of ICD and CRT-D devices under conscious sedation is certainly not free of complications. There are many clinical factors that predispose these patients to the

**Table 2** Treatment of hypotension

| | ICD Group (N=40) | CRT-D Group (N=56) | p-value |
|---|---|---|---|
| Normal saline infusion | 30 (75%) | 32 (57.14%) | 0.07 |
| Vasoactive drugs | | | |
| Ephedrine | 4 (10%) | 1 (1.78%) | |
| Phenylephrine | 6 (15%) | 19 (33.92%) | |
| Dopamine | | 2 (3.57%) | |
| Epinephrine | | 2 (3.57%) | |

development of hypotension, which may progress to hemodynamic collapse. Patients receiving these devices usually have advanced heart failure, low ejection fraction, poor cardiac reserve and are on several medications that interfere with mounting a physiologic response to hemodynamic embarrassment [6]. Low EF and high NYHA class correlates directly to the development of hypotension during the procedure as shown in this study. Furthermore, it has been suggested that pacing the epicardial inferior postero-lateral surface of the left ventricle via the coronary sinus during CRT-D device implantation may lead to stimulation of the unmyelinated C fibers. The resultant induction of Bezold-Jarisch reflex may result in a drop in heart rate and blood pressure and even asystole [6,7]. Whether the Bezold-Jarisch reflex plays a role in causing hypotension during CRT-D implantation is not known.

We report a significant incidence of hypotension in patients undergoing these procedures (40–57%). This may appear relatively high in the view of most implanting physicians. However, we don't think this is an anomaly and may be due to the accurate, continuous assessment of blood pressure by an arterial cannula in our patients. Most laboratories monitor blood pressure non-invasively during implant procedures using a blood pressure cuff, which is cycled every few minutes and it may be that relatively short episodes of hypotension are not detected. It is also possible that some episodes of hypotension in our patients may have resolved spontaneously, but were treated because the blood pressure fall was displayed graphically on the arterial line tracing and triggered a therapeutic intervention. In our study population, 25–35% of patients required relatively small doses of vasopressors (a single intravenous bolus of 5 mg ephedrine or a single intravenous bolus of 100mcg of phenylephrine) to normalize the blood pressure. None of the patients had pneumotharax, hemothorax, excessive blood loss, required transfusion in the post-operative period or had prolonged hospital stay. None of our patients had an adverse event attributable to intraoperative hypotension.

Prolonged procedure time mandates a higher dose of anesthetics and may lead to undesirable hemodynamic consequences. Our study shows a direct effect of procedural time and dose of propofol on the development of hypotension. Patients undergoing ICD implantation received a significantly lower dose of propofol compared to those undergoing CRT-ICD implantation, owing to a significantly shorter duration of procedures (Fig. 1).

Propofol (2, 6-diisopropylphenol) is a potent short-acting intravenous hypnotic agent, which is widely used as a short-acting anesthetic agent for cardiovascular procedures. Present formulations consist of 1% or 2% propofol, 1.2% in egg phosphatide, 2.25% in glycerol and 10% soybean oil [7]. Propofol directly activates GABA (A) receptors. In addition, propofol inhibits the NMDA receptors and modulates the calcium influx through slow calcium ion channels. Propofol has a rapid onset of action with a dose-related hypnotic effect. It has a rapid recovery even after prolonged use. Pharmacodynamic properties of propofol are dependent upon the therapeutic blood propofol concentrations. The ratio of hydroxylation and glucuronidation metabolites of propofol shows an inter-patient variability with no correlation with the dose of propofol. The variation of the metabolite profile does not seem to play an extended role in the pharmacokinetic variability [8].

Steady state propofol blood concentrations are generally proportional to infusion rates. Undesirable side effects such as cardio-respiratory depression are likely to occur at higher blood concentrations, which result from bolus dosing or rapid increase in infusion rate [9–13].

Propofol has been shown to cause hypotension in many studies. There are numerous case reports about fatal cardiovascular collapse due to propofol infusion [14–17]. Advanced age, NYHA class III and IV and a baseline mean arterial pressure of less than 70 mm Hg has been shown to be associated with hypotension after induction with propofol [18]. In their review and analysis, the Food and Drug Administration reports cardiac dysfunction (45%), and hypotension (30%) as the cause of death with use of propofol for nonprocedural sedation [19]. They concluded that higher doses of propofol, in higher concentrations, and usually for longer durations increase the risk of complications, and hence suggested that the doses of propofol should be kept as low as effectively possible [19]. Biologic effect of underlying mechanism can be due to negative inotropic effect of propofol. It has been shown to decrease cardiac output by 17.3% and systemic vascular resistance by 11.6%, resulting in decreased systolic and diastolic blood pressures [20]. Propofol acts in a dose-dependent manner to antagonize beta-receptors, and linearly reduce ventricular performance with higher concentration [21,22]. Patients in our study had comparable baseline demographics in both groups with reference to age, gender, underlying rhythm and etiology of left ventricular dysfunction.

The mean creatinine clearance was greater in the non-hypotensive subset in both the groups. The creatinine clearance in the CRT-D group was significantly greater in the non-hypotensive subset compared to hypotensive subgroup. This was a significant factor predicting the development of hypotension in both groups.

These results support the findings of previous studies depicting cardiovascular depression due to propofol. While CRT-D may improve quality of life by achieving hemodynamic compensation in patients with refractory heart failure, the procedure is not free of risks. Propofol should be used with caution in patients with a confluence of risk factors: advanced heart failure, poor EF and severe renal dysfunction. Effective doses of propofol should be kept as

low as possible. Further large studies are required to better understand the underlying mechanisms of hemodynamic compromise during such procedures. Responses to other anesthetic agents with less cardiovascular side effects also need to be studied during such procedures.

## 5 Limitations

Our study suggests that hypotension is more common in patients with advanced heart failure, poor ejection fraction, advanced renal dysfunction, higher propofol dose and longer procedure times, but it has the usual limitations of a single-center, retrospective study. The lack of a comparison group sedated with a regimen excluding propofol is a major limitation. Furthermore, the use of continuous intra-arterial pressure monitoring may have led to a bias towards treating hypotension earlier than otherwise really needed. As a result, it is likely that there may have been an overuse of vasopressors and fluid boluses reported.

While considerable attention is devoted to improving the technology that enables delivery of CRT-D, more effort is needed to ensure patient safety and lower the risks of complications.

## 6 Recommendations

Intra-arterial blood pressure monitoring is not common during ICD and CRT-D implantations. In general, as operators have gained experience and with improvement in technology to achieve left ventricular pacing, these procedures have become shorter in duration and more successful. Because of short procedure times, brief episodes of hypotension may be well tolerated. On occasion, complications may ensue. We recommend consideration of accurate intra-arterial blood pressure monitoring during these procedures rather than a non-invasive blood pressure cuff and prompt treatment of hypotension using fluid boluses or small doses of vasopressors.

## 7 Summary

Hypotension is a common occurrence during defibrillator implantation performed using propofol. Risk factors for significant hypotension include: higher NYHA class, lower left ventricular ejection fraction, lower creatinine clearance, higher doses of propofol and longer procedure times.

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**Conflict of interest** The authors do not have any conflict of interest related to this manuscript.

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