

# Synopsis of Most Relevant Articles on Cardiac Arrhythmias

Sinopse de Artigos Mais Relevantes em Arritmias Cardíacas

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## Chronotropic Incompetence with Risk Predictor In Children and Young Adults With Catecholaminergic Polymorphic Ventricular Tachycardia\*

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially lethal hereditary channelopathy. Recent data suggest an unfavorable natural history, with almost 80% of patients suffering a life-threatening cardiac event close to 40 years. The ergometric test (ET) provides information on ventricular ectopias (VE) and their density as a predictor of cardiac events, chronotropic incompetence (CI), or attenuated heart rate (HR) are also prognostic in other conditions. The authors propose, therefore, that CI during exercise can predict a higher arrhythmic incidence in patients with CPVT. The study was a retrospective analysis of young patients ( $\leq 21$  years) with CPVT in tertiary centers such as the British Columbia Children's Hospital and the Monroe Carell Jr. Children's Hospital in Vanderbilt. Two ETs per patient were analyzed (14 without therapy and 17 in maximum therapy), with HR and blood pressure (BP) monitoring; the maximum effort achieved was measured in metabolic equivalents (METs) and total exercise time (in seconds). The score of ventricular arrhythmias (SVA) was determined according to: no VE = 0, isolated premature ventricular beats = 1, bigeminy = 2, pairs = 3, and nonsustained ventricular tachycardia = 4. The mean age at the first ET was 12 years, with 45% male patients, with syncope reported in six patients (30%) and sudden cardiac death (SCD) in eight patients (40%), while the remaining six (30%) were asymptomatic and were submitted to family genetic screening. The causes for interrupting the ET in the group without medication were fatigue (40%), cardiac arrhythmia, bidirectional VT in 40%, and target HR reached in 20%; 5 out of 14 patients without therapy presented CI (36%). Patients with CI were those with worse SVA when compared to patients with normal chronotropism ( $3.4 \pm 0.6$  vs  $1.4 \pm 0.6$ ;  $P = 0.046$ ), lower resting diastolic BP ( $65 \pm 3$  vs  $74 \pm 2$ ;  $P = 0.045$ ), lower peak systolic BP ( $133 \pm 10$  vs  $168 \pm 10$ ;  $P = 0.041$ ) and lower delta systolic BP (peak systolic BP minus resting systolic BP;  $24 \pm 8$  vs  $59 \pm 11$ ;  $P = 0.047$ ). Of patients with medication, 10 out of 17 (59%) had CI (HR reserve  $\leq 62\%$ ); the causes for interruption of ET were fatigue in 80%, shortness of breath in 10%, and anxiety in the other 10%. An important detail about the ET was that it was interrupted/limited by symptom/arrhythmia and not target HR. There was no difference in SVA between patients with CI and those with normal chronotropism in maximum therapy ( $P = 0.05$ ). The patients with CI in maximum therapy continued to present lower peak systolic AP ( $126 \pm 6.2$  vs.  $151.4 \pm 9.5$ ;  $P = 0.033$ ) compared to patients without CI. There was no association between age, exercise duration, METs attained, HR at rest, systolic AP at rest, diastolic AP at rest, and delta systolic AP. Beta-blocker therapy showed a depressant effect on the peak HR to effort in patients with CI (no therapy:  $161.2 \pm 5.4$  vs maximum therapy:  $128.5 \pm 6.4$ ;  $P = 0.0058$ ) and normal chronotropism (no therapy:  $197.8 \pm 3.3$  vs maximum therapy:

157.1 ± 3.4;  $P < 0.0001$ ). Nine out of ten patients (90%) with CPTV and CI in maximum therapy required additional therapy besides beta-blocker, compared to 43% with normal chronotropism ( $P = 0.042$ ), with no differences regarding cardioverter-defibrillator implantation. The authors conclude that the ET promotes valuable clinical information apart from the diagnosis of CPTV, with CI being a risk marker for CPTV, which seems to be attenuated with antiarrhythmic therapy. A relatively hypotensive response to exercise can be a new prognostic marker. The findings of the study imply that the autonomous nervous system plays a role in modulating the disease.

\*Franciosi S, Roston TM, Perry FKG, Knollmann BC, Kannankeril PJ, Sanatani S. Chronotropic incompetence as a risk predictor in children and young adults with catecholaminergic polymorphic ventricular tachycardia. *J Cardiovasc Electrophysiol.* 2019;30(10):1923-9. <https://doi.org/10.1111/jce.14043>

## Effects of Direct Oral Anticoagulants, Warfarin and Antiplatelet Agents on Risk of Device Pocket Hematoma. Combined Analysis of The Bruise Control 1 and 2\*

Pocket hematoma incidence varies widely: 1.2% when no anticoagulant is in use, from 2.3 to 6.5% with continued warfarin therapy and from 7 to 16% during heparin bridging. The study Bruise Control 1 (BC1) showed an increase of more than seven times in the risk of device infection in clinically significant hematomas (CSH), which requires reoperation or result in longer hospitalization; if reintervention is necessary, the chance of infection increases by more than 15 times. BC1 showed 80% less device pocket hematoma when the surgery was performed without interruption of warfarin compared to the bridging strategy with heparin (3.5 and 16%, respectively). The study Bruise Control 2 (BC2) evaluated the use of direct oral anticoagulants (DOACs), and was early interrupted due to no difference in CSH between the continued (2.1%; 95% CI, 0.9-4.3%) and the interrupting DOAC (2.1%; 95% CI, 0.9-4.3%;  $P = 0.97$ ). The study in question evaluated data from BC1 and BC2 and the effects of concomitant use of antiplatelet in HCS, and aimed at understanding the risk of wound hematoma in patients treated with DOAC versus continued warfarin; both studies were multicenter, randomized, single-blind. The study included 1,343 patients: 681 from BC1 and 662 from BC2. BC1 enrolled patients with 5% or more annual predictive risk of thromboembolism, using warfarin and planning elective device implantation; BC2 enrolled patients with nonrheumatic atrial fibrillation and  $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$  treated with DOAC and elective implants. Among the 1,343 patients included, 408 (30.4%) were identified as using at least one antiplatelet at the time of surgery, and 935 patients (69.6%) were not using it. Of the former, 383/408 (93.9%) used aspirin, 50/408 (12.3%) clopidogrel and 25/408 (6.1%) both. The primary outcome of CSH occurred in 40/408 (9.8%) patients with antiplatelet versus 40/935 (4.3%) in the group without antiplatelet ( $P < 0.001$ ), generating more reoperation (2% vs 0.6%) and the need to stop oral anticoagulation (9.1% vs 3.9%); in patients with double antiplatelet therapy the occurrence of CSH was 2/25 (8%) compared to 38/383 (9.9%) using an antiplatelet ( $P = 1.0$ ). In multivariate analysis, there was no difference in CSH between interrupted or continuous DOAC versus continuous warfarin (odds ratio, OR, 0.858; 95% CI, 0.375-1.963;  $P = 0.7174$ ). The use of antiplatelet in addition to discontinued or continued DOAC was a predictor of CSH (OR, 1.965; 95% CI, 1.202-3.213;  $P = 0.0071$ ). The authors conclude that the concomitant use of antiplatelet therapy doubled the risk of CHS in the patients of both BC1 and BC2 studies, and the interruption of antiplatelet as part of the perioperative strategy should be considered with caution.

\*Essebag V, Healey JS, Joza J, Nery PB, Kalfon E, Leiria TLL, et al. Effect of Direct Oral Anticoagulants, Warfarin, and Antiplatelet Agents on Risk of Device Pocket Hematoma. Combined Analysis of BRUISE CONTROL 1 and 2. *Circ Arrhythm Electrophysiol.* 2019;12(10):1-8. <https://doi.org/10.1161/CIRCEP.119.007545>

## Direct Current Cardioversion of Atrial Fibrillation in Patients With Left Atrial Appendage Occlusion Devices\*

Direct current cardioversion (DCCV) is a common strategy for rhythm control in atrial fibrillation (AF) and atrial flutter (AFL) of symptomatic patients, associated with a small risk of stroke or systemic embolism, being around 0.3 to 1%. In the absence of anticoagulation, the risk of these complications increases more than twice. The use of left atrial appendage occlusion (LAAO) devices emerged as an alternative for the prevention of systemic embolization in patients with AF who are not candidates for prolonged use of oral anticoagulants (OAC); in these patients, there are no long-standing data related to the safety and viability of DCCV after LAAO implantation. This was a retrospective, multicenter study involving consecutive patients in AF/AFL with LAAO by the Watchman device (Boston Scientific, Marlborough, Massachusetts) undergoing elective DCCV between July 2013 and July 2017. Clinical outcomes included the safety and feasibility of performing DCCV after LAAO implantation. All patients received an antithrombotic regimen including six weeks of aspirin 81 mg per day with warfarin (INR between 2-3)/ DOAC; patients migrated to aspirin 81 mg and clopidogrel 75 mg per day after a new transesophageal echocardiogram (TEE) or computed tomography (CT), demonstrating a satisfactory position of the device, without thrombus related to the device (TRD) or leak around the device  $\leq 5$  mm. In the sequence, the patients started only with 81 mg aspirin after six months and a new TEE or CT. In respect to the DCCV, all patients were submitted to a new ET echocardiogram just before it and, if some of the previously mentioned conditions did not coincide, the DCCV was not performed, and the patients maintained OAC for other 4-6 weeks with a new review examination. A total of 148 patients were enrolled, with a mean age of  $72 \pm 7$  years, 59% male and 49% with paroxysmal AF; the CHA<sub>2</sub>DS<sub>2</sub>-VASC and mean HAS-BLED were  $3.8 \pm 1.7$  and  $3.4 \pm 1.6$ , respectively. At the time of DCCV, 34% (51 of 148) were with OAC, 30% (44 of 148) with dual antiplatelet therapy, and 36% (53 of 148) with only aspirin 81 mg per day. Immediately after the DCCV, 22% (32 of 148) restarted OAC with a mean length of use of 12 weeks after DCCV, and patients taking OAC were submitted to DCCV earlier than those taking antiplatelets (3.6 months [0.7 to 8.6 months] versus 8.6 months [2.5 to 13.3 months];  $P = 0.003$ ). There was no thromboembolic complication related to DCCV, but three transient ischemic attacks after 3.5 months of DCCV. There were 4% (6 out of 148) of bleeding, four greater (fatal or with a drop of hemoglobin  $>3$  g/dl), and two smaller; more events occurred in patients maintained with OAC but without statistically significant difference. The authors conclude that preliminary DCCV results in high-risk patients with AF and after LAAO without the need for OAC are favorable if the TEE showed good device position, absence of TRD, and leak  $< 5$  mm, however, further studies should be performed.

\*Sharma SP, Turagam MK, Gopinathannair R, Reddy V, Kar S, Mohanty S, et al. Direct Current Cardioversion of Atrial Fibrillation in Patients with Left Atrial Appendage Occlusion Devices. *J Am Coll Cardiol*. 2019;74(18):2268-74. <https://doi.org/10.1016/j.jacc.2019.08.1045>

## Radiofrequency Ablation versus Cryoablation in The Treatment of Paroxysmal Atrial Fibrillation: A Meta-Analysis\*

Atrial fibrillation (AF) is a common arrhythmia affecting up to 2% of the population, commonly affecting the elderly, with 26% risk in men and 23% risk in women at the age of 80. The first line in AF treatment includes pharmacological agents, which focus on heart rate (HR) control, rhythm control, and oral anticoagulation (OAC). In patients with paroxysmal AF refractory to drugs, catheter ablation with pulmonary veins isolation is the standard therapy; this can be done with radiofrequency (RF), with a heat injury, or with cryoablation (CRIO), i.e., freezing injury. RF is considered the standard therapy and is more widely used than CRIO; however, it is longer and requires extensive training, while CRIO has similar effectiveness to RF with lower complication rates. Currently, the best treatment for AF ablation is under debate; previous meta-analyses have been done, but

have resulted in inconclusive or have included a large number of study designs, limiting the overall quality and external validity. The objective of the study was to compare the long-standing effectiveness measured by AF-free survival at 12-months follow-up and complications related to the two methods. All studies randomly allocated patients  $\geq 18$  years treated with RF or CRIO, excluding nonrandomized studies. Primary outcomes were long-term freedom from atrial fibrillation at 12-month follow-up and overall postoperative complication rates; secondary outcomes were procedure time, radioscopy, and ablation. A systematic literature survey identified a total of 247 articles; after an initial title and abstract screening, 17 articles were considered and retrieved to assess their eligibility through full-text review. Of these, a total of eight met the prespecified inclusion criteria and were included in the review, including 1,548 patients undergoing RF or CRIO ablation. All studies were published between 2012 and 2015 and were conducted at centers across continental Europe, the UK, and Russia. Seven compared CRIO with RF using an irrigated catheter, while one compared CRIO with phased RF (phased duty-cycled). Regarding the AF-free survival of the treated patients, 53% (393/741) submitted to CRIO ablation, and 53% (399/751) submitted to RF developed AF in a period  $\geq 12$  months, without differences between the type of energy used (odds ratio, OR = 0.98, confidence index, CI = 0.67-1.43,  $P = 0.9$ ) and, even withdrawing the study with a phased catheter, there was no difference in the energies used. Regarding the procedure time, in general, the CRIO was faster in 4.08 minutes; however this difference did not reach statistical significance. Six studies evaluated the radioscopy time ( $n = 1,204$ ), being 33.11 minutes with CRIO and 31.94 minutes with RF, also without reaching statistical significance (mean difference, MD = 1.17, CI = -4.94-7.28,  $I^2 = 87\%$ ,  $P = 0.71$ ). Two studies evaluated the ablation time ( $n = 155$ ), 99.02 minutes with CRIO and 91.06 minutes with RF, also without reaching statistical significance (MD = 7.97, CI = -35.15-51.09,  $I^2 = 95\%$ ,  $P = 0.72$ ). Seven studies analyzed postoperative complications with both energy sources ( $n = 1,492$ ). Despite the type of complication and its transitory nature, CRIO presented 1.9 times more chance of events when compared to RF; however, this difference did not reach statistical significance, and the data remained unchanged after sensitivity analysis. Phrenic nerve injury was 10.3 times more likely to occur with CRIO, and five studies reported it as transient and resolved in 12 months, being permanent in one study and one patient. Regarding cardiac tamponade, there were no differences between the procedures (OR = 0.39, CI = 0.11-1.40,  $I^2 = 0\%$ ,  $P = 0.15$ ). The authors conclude that the results of this meta-analysis show similar overall success rates over 12 months, with comparable radioscopy rates, procedure times, and long-term complications between CRIO and RF. Given the outcome, operators should choose the technology based on the patients' characteristics and preferences as well as operator experience and preference.

\*Hachem AH, Marine JE, Tahboub HA, Kamdar S, Kanjwal S, Soni R, Kanjwal K. Radiofrequency Ablation versus Cryoablation in the Treatment of Paroxysmal Atrial Fibrillation: A Meta-Analysis. *Cardiol Res Pract.* 2018;1-10. <https://doi.org/10.1155/2018/6276241>

## Mortality Risk Following Catheter Ablation of Atrial Fibrillation\*

Catheter ablation (CA) is already established as an important treatment for symptomatic atrial fibrillation (AF), leading to significant improvement in the quality of patients' lives. Moreover, in patients with systolic heart failure (HF), the ablation proved superior to pharmacological therapy in reducing overall mortality and hospitalization for congestive heart failure (CHF). As procedures have been gradually increasing, there is a need to understand the serious complications rates in the real world, and recent studies suggest a greater tendency of ablation-related complications despite advances in catheter technology and operator experience. To date, in-hospital death rates range from 0 to 0.8%. However, these data are related to academic centers, regional databases, single-payer health care systems, and restricted national admissions to ablation. Since complications such as esophageal injury, sepsis, and CHF can occur after ablation, the authors raised the hypothesis that a proportion of events would occur during readmission and not during admission to the procedure and, using a representative national database, sought to

promote real-world evidence on rates, trends and predictors of early mortality after AF ablation, defined by combined in-hospital mortality from the initial admission (to procedure) or readmission 30 days after the procedure. All data were obtained from the US Agency for Healthcare Research in Quality (AHRQ) from 2010 to 2015. The annual volume of ablation for AF was determined on an annual basis by calculating the total number of procedures performed in a particular institution in a given year. The primary outcomes were early overall mortality after ablation for AF, defined as mortality occurring at initial admission or readmission 30 days after the procedure. Other outcomes included perforation/tamponade, other iatrogenic cardiac complications, central nervous system complications, vascular complications, and pneumothorax. A total of 60,203 admissions were recorded; the overall early mortality rate after ablation was 0.46% (95% confidence interval, CI: 0.37 to 0.52%). Of the 276 early deaths, 126 (45.7%) occurred in the initial hospitalization and 150 (54.3%) in readmission; compared to survivors, the patients who died were older and had higher comorbidities with CHF, coronary artery disease, previous pacemaker implantation, pulmonary hypertension, chronic lung disease, anemia and coagulopathy (40.1% versus 14.4% with Elixhauser comorbidity index  $\geq 4$ ;  $P < 0.001$ ). Patients who died early had their procedures performed in smaller centers resided in lower-income areas and had longer periods of hospitalization. The global rate of any procedure-related complication was 6.7%, and patients who died early had greater procedure-related complications (25.6 versus 6.6%;  $P < 0.001$ ), with more cardiac perforation, other cardiac complications, neurological complications, and pneumothorax. Regarding predictors of early mortality after AF ablation, after adjustment for age, comorbidities and hospital characteristics, procedure complications were independently associated with early mortality (adjusted odds ratio, aOR: 4.06; CI = 95%: 2.40 to 6.85;  $P < 0.001$ ), in addition to CHF (aOR: 2.20; CI = 95%: 1.20 to 4.03;  $P = 0.011$ ), anemia (aOR: 1.83; CI = 95%: 1.13 to 2.96;  $P = 0.015$ ), coagulopathy (aOR: 2.14; CI = 95%: 1.04 to 4.39;  $P = 0.046$ ) and age (aOR: 1.04; CI = 95%: 1.00 to 1.07;  $P = 0.046$ ). Finally, patients submitted to ablation in low-volume centers presented higher chances of early mortality (aOR: 2.35; CI = 95%: 1.33 to 4.15;  $P = 0.003$ ), in these cases the highest independent predictors: cardiac perforation, other cardiac complications and neurological complications such as transient ischemic attack/stroke. The causes of readmission in the 150 patients with death were cardiac (30%), infectious (30%), respiratory (17%), and neurological (12%). The four most common diagnoses were septicemia (15%), CHF (15%), pneumonia (7.4%) and stroke (5.9%) and the patients were more commonly submitted to mechanical ventilation, blood transfusion, echocardiogram, endoscopy, dialysis, chest tube installation, right heart catheterization, bronchoscopy, mechanical circulatory support, and thoracentesis. The 0.46% rate found in this study exceeds the procedure-related mortality rates reported by other major studies. In a study based on international research with 20,825 procedures between 2003 and 2006, the mortality rate was 0.15%. Another finding of this study was a growing increase in early mortality rates between 2010 and 2015, which can be explained by two important factors: first, higher rates of comorbidities were identified as CHF, coronary, pulmonary and chronic renal disease, explaining in part the growth of 4.8 to 7.8% in the cited years; second, the volume of ablation for AF as well as the number of institutions increased in the recent years. Consequently, more procedures are being performed in low-volume centers, which are associated with higher complication rates. Regarding the main cause of readmission, septicemia, the authors could not obtain data to prove whether it was related to atrioesophageal fistula, as there was no specific coding in the international code of diseases. The authors conclude that in this contemporary, nationally representative, real-world cohort, early mortality after AF ablation was 0.46%, with most of the deaths occurring in readmission within 30 days after the procedure. Complications in the initial procedure were independent predictors of early mortality. Sepsis and CHF were the main causes of readmission associated with mortality, and the implementation of strategies to reduce complications in procedures, optimize management of CHF and reduce nosocomial infections can help reduce early mortality after AF ablation.

\*Cheng EP, Liu CF, Yeo I, Markowitz SM, Thomas G, Ip JE, et al. Risk of Mortality Following Catheter Ablation of Atrial Fibrillation. *J Am Coll Cardiol.* 2019;74(18):2254-64. <https://doi.org/10.1016/j.jacc.2019.08.1036>