Site-Specific Effects of Dobutamine on Cardiac Conduction and Refractoriness

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Abstract

Background: Isoproterenol, a non-specific beta agonist, is commonly used during electrophysiology studies (EPS). However, with the significant increase in the price of isoproterenol in 2015 and the increasing number of catheter ablations performed, the cost implications cannot be ignored. Dobutamine is a less expensive synthetic compound developed from isoproterenol with a similar mechanism to enhance cardiac conduction and shorten refractoriness, thus making it a feasible substitute with a lower cost. However, the use of dobutamine for EPS has not been well-reported in the literature. **Objective:** To determine the site-specific effects of various doses of dobutamine on cardiac conduction and refractoriness and assess its safety during EPS. **Methods:** From February 2020 to October 2020, 40 non-consecutive patients scheduled for elective EPS, supraventricular tachycardia, atrial fibrillation, and premature ventricular contraction ablations at a single center were consented and prospectively enrolled to assess the effect of dobutamine on the cardiac conduction system. At the end of each ablation procedure, measures of cardiac conduction and refractoriness were recorded at baseline and with incremental doses of dobutamine at 5, 10, 15, and 20 mcg/kg/min. For the primary analysis, the change per dose of dobutamine from baseline to each dosing level of dobutamine received by the patients, comparing atrioventricular node block cycle length (AVNBCL), ventricular atrial block cycle length (VABCL) and sinus cycle length (SCL), was tested using mixed-effect regression. For the secondary analysis, dobutamine dose level was tested for association with relative changes from baseline of each electrophysiologic parameter (SCL, AVNBCL, VABCL, atrioventricular node effective refractory period (AVNERP), AH, QRS, QT, atrial effective refractory period (AERP), ventricular effective refractory period (VERP), using mixed-effect regression. Changes in systolic and diastolic blood pressures were also assessed. The Holm-Bonferroni method was used to adjust for multiple testing. **Results:** For the primary analysis there was no statistically significant change of AVNBCL and VABCL relative to SCL from baseline to each dose level of dobutamine. The SCL, AVNBCL, VABCL, AVNERP, AERP, VERP and the AH, and QT intervals all demonstrated a statistically significant decrease from baseline to at least one dose level with incremental dobutamine dosing. Two patients (5%) developed hypotension during the study and one patient (2.5%) received a vasopressor. Two patients (5%) had induced arrhythmias but otherwise no major adverse events were noted. **Conclusion:** In this study, there was no statistically significant change of AVNBCL and VABCL relative to SCL from baseline to any dose level of dobutamine. As expected, the AH and QT intervals, and the VABCL, VERP, AERP and AVNERP all significantly decreased from baseline to at least one dose level with an escalation in dobutamine dose. Dobutamine was well-tolerated and safe to use during EPS.

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Short Title: The Effects of Dobutamine on the Cardiac Conduction System

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Objective: To determine the site-specific effects of various doses of dobutamine on cardiac conduction and refractoriness and assess its safety during EPS.

Methods: From February 2020 to October 2020, 40 non-consecutive patients scheduled for elective EPS, supraventricular tachycardia, atrial fibrillation, and premature ventricular contraction ablations at a single center were consented and prospectively enrolled to assess the effect of dobutamine on the cardiac conduction system. At the end of each ablation procedure, measures of cardiac conduction and refractoriness were recorded at baseline and with incremental doses of dobutamine at 5, 10, 15, and 20 mcg/kg/min. For the primary analysis, the change per dose of dobutamine from baseline to each dosing level of dobutamine received by the patients, comparing atrioventricular node block cycle length (AVNBCL), ventricular atrial block cycle length (VABCL) and sinus cycle length (SCL), was tested using mixed-effect regression. For the secondary analysis, dobutamine dose level was tested for association with relative changes from baseline of each electrophysiologic parameter (SCL, AVNBCL, VABCL, atrioventricular node effective refractory period (AVNERP), AH, QRS, QT, atrial effective refractory period (AERP), ventricular effective refractory period (VERP), using mixed-effect regression. Changes in systolic and diastolic blood pressures were also assessed. The Holm-Bonferroni method was used to adjust for multiple testing.

Results: For the primary analysis there was no statistically significant change of AVNBCL and VABCL relative to SCL from baseline to each dose level of dobutamine. The SCL, AVNBCL, VABCL, AVNERP, AERP, VERP and the AH, and QT intervals all demonstrated a statistically significant decrease from baseline to at least one dose level with incremental dobutamine dosing. Two patients (5%) developed hypotension during the study and one patient (2.5%) received a vasopressor. Two patients (5%) had induced arrhythmias but otherwise no major adverse events were noted.

Conclusion: In this study, there was no statistically significant change of AVNBCL and VABCL relative to SCL from baseline to any dose level of dobutamine. As expected, the AH and QT intervals, and the VABCL, VERP, AERP and AVNERP all significantly decreased from baseline to at least one dose level with an escalation in dobutamine dose. Dobutamine was well-tolerated and safe to use during EPS.

Key words: Dobutamine, electrophysiology study, supraventricular tachycardia, cardiac conduction, cost analysis

Introduction

Isoproterenol is a non-specific beta agonist commonly used during electrophysiology studies (EPS). Its β1-stimulation promotes tachyarrhythmia induction by improving cardiac conduction and shortening AV nodal refractoriness. However, the financial burdens of using isoproterenol are significant given the high cost of the medication and the increasing number of catheter ablations.[1,2]

Dobutamine is a less expensive synthetic compound developed from isoproterenol that is predominantly a β1-agonist with mild β2 and α1-activities.[3] It has been well-studied and used in cardiac stress imaging as well as treatment for cardiogenic shock.[4] Therefore, dobutamine is a feasible, less expensive alternative to isoproterenol. However, its use for EPS has not been extensively studied.

The purpose of this study was to determine the site-specific effects of various doses of dobutamine on cardiac conduction and refractoriness and assess its safety during EPS.

Methods

This study was approved by the Institutional Review Board of Northwell Health and exempted from the investigational new drug (IND) based upon a Food and Drug Administration (FDA) review.

From February 2020 to October 2020, 40 non-consecutive patients scheduled for elective EPS, supraventricular tachycardia (SVT), atrial fibrillation (AF), and premature ventricular contraction (PVC) ablations at a single center were consented and prospectively enrolled for the use of dobutamine. The inclusion criteria were patients between the ages of 18 and 80 and those undergoing EPS. Patients were excluded from the study for the following conditions: (1) hypertrophic obstructive cardiomyopathy or other forms of left ventricular outflow tract obstruction, (2) severe aortic stenosis, (3) prior sustained ventricular tachycardia or ventricular fibrillation, (4) prior allergic reaction to dobutamine or sulfates, and (5) pregnancy.

All procedures were performed in the EP laboratory under general anesthesia or conscious sedation monitored by an anesthesiologist. Standard multi-electrode catheters were inserted via the femoral vein and positioned fluoroscopically at the His-bundle position, coronary sinus, and right ventricular apex. Stimulation was performed with a programmable stimulator EP-4^{TM} (St. Jude Medical, Little Canada, MN, USA). The procedures were performed by three experienced electrophysiologists and the standard EPS protocol was performed as previously reported.[5]

At the conclusion of each ablation, the baseline blood pressure and the following parameters were recorded: (1) sinus cycle length (SCL), (2) AH interval, (3) HV interval, (4) QRS duration, (5) QT interval, (6) AV node block cycle length (AVNBCL), (7) AV node effective refractory period (AVNERP), and (8) VA block cycle length (VABCL), (9) atrial effective refractory period (AERP) and (10) ventricular effective refractory periods (VERP). Dobutamine was then infused at 5, 10, 15, and 20 mcg/kg/min with a waiting period of five minutes before the blood pressure and the same parameters noted from baseline were recorded. Blood pressures were recorded from an arterial line or manual cuff at five-minute interval. Electrogram intervals were measured using CardioLab^{TM} (GE Healthcare, Chicago, IL, USA). The study endpoint was at protocol completion with measurements at baseline and at each incremental dose of dobutamine. If any sustained arrhythmia was induced, the arrhythmia was ablated and the study was stopped.

Stimulation was performed by pacing at the coronary sinus and the right ventricular apex at cycle lengths just shorter than the prevailing sinus cycle length, and then at progressively shorter cycle lengths to the point of AV or VA block. Programmed stimulation was then performed at each site beginning with an 8-beat drive train at 600 msec in the atrium and the ventricle with single extrastimuli beginning in late diastole, and then progressively earlier in 10-msec decrements (with increasing doses of dobutamine, the drive train cycle was decreased to avoid competition during sinus tachycardia), which understandably affected atrial, AV nodal and ventricular refractoriness. The SCL, and AH and HV intervals were measured from an average

of at least ten consecutive intervals recorded from the His-bundle catheter. The AVNBCL and VABCL were determined as the longest pacing cycle length from the coronary sinus and right ventricular apex, respectively, which resulted in AV nodal block during gradually increasing pacing rates. The anterograde AVNERP was measured as the longest A1-A2 interval (measured in the His bundle recording), at a drive cycle length of 600 msec, in which the A2 failed to propagate through the AV node. Similarly, the retrograde AVNERP was the longest V1-V2 coupling interval, at a drive cycle length of 600 msec, at which the premature stimulus failed to propagate to the atrium. Pacing cycle lengths of 600, 500, 450 and 400 msec were used to measure the refractory periods, in view of the shortening of the sinus cycle length in response to dobutamine. Although we understand the limitation of pooling the refractory periods with varying drive cycle lengths, we preferred reporting a single mean refractory period for each dose of dobutamine.

Statistical Methods:

Retrospective data of the use of dobutamine in our EP lab since March 2015 was used for the sample size calculation, which showed that the mean and standard deviation for the difference between the change as a percent from baseline in the SCL and the change from baseline in the AVNBCL is 7.7% ± 16.0% at 20 mcg/kg/min of dobutamine. We enrolled 40 patients based on the finding that a study of 37 patients yields 80% power with respect to the primary endpoint with an alpha of 0.05 using a paired 2-tail t-test.

The change per dose of dobutamine from baseline to each dosing level of dobutamine received by the patients, comparing AVNBCL, VABCL and SCL, was tested using mixed-effect regression.

Dobutamine dose level was tested for association with relative changes from baseline of each electrophysiologic parameter (SCL, AVNBCL, VABCL, AVNERP, AH and QT intervals) using mixed-effects regression. The Holm-Bonferroni method was used to adjust for multiple testing. Estimates of the change from baseline in each electrophysiologic parameter at each dose of dobutamine were provided along with 99% confidence intervals and plots.

Results

Between February 2020 to October 2020, 40 non-consecutive patients median age 63 years (IQR 55-69), 11 (28%) females, scheduled for elective EP procedures at a single center consented and received dobutamine at the end of the procedure for EPS. The patient demographics and the diagnoses for the procedure indications are listed in Table 1.

There was no significant difference in the change in AVNBCL relative to the SCL and the change in the VABCL relative to the SCL at each incremental dose of dobutamine (Tables 2, 3 and 4, Figures 1 and 2).

The SCL shortened with incremental doses of dobutamine (Table 2, 3, 4, Figure 1). The change only became statistically significant at 10 mcg/kg/min and greater doses. The largest percentage decrease in the SCL from one consecutive dose escalation to the next was noted between 5 and 10 mcg/kg/min. Similarly, antegrade and retrograde AV nodal conduction shortened with each dose of dobutamine and the largest decrease in AVNBCL and VABCL between consecutive dose escalations was also noted between 5 and 10 mcg/kg/min (Table 2, 3, 4, Figures 2). The AH interval shortened at 15 mcg/kg/min and greater doses (Tables 2, 3, 4, Figure 3) but the HV interval did not show evidence of change (Tables 2, 3, 4, Figure 4). As expected, the QRS duration did not change significantly from baseline to each incremental dose of dobutamine (Tables 2, 3, 4, Figure 5). The QT interval decreased with escalation in dobutamine dose starting at 15 mcg/kg/min, an expected finding given that the sinus cycle length decreased with higher doses of dobutamine, and the QT was not corrected for rate (Tables 2, 3, 4, Figure 5).

The effects of dobutamine on the anterograde AVNERP could not be determined consistently because, in many cases, it was shorter than the AERP. The SCL shortened with each dobutamine dose escalation and required shortening of the drive cycle length when measuring effective refractory periods. Shorter drive train cycle length also led to AV nodal block precluding measurement of the AVNERP. AVNERP was not reported when it was shorter than the AERP. The retrograde AVNERP could not be assessed consistently because retrograde conduction was limited by His-Purkinje refractoriness or inability to see a stable retrograde His

deflection. The AVNERP data were included in the analysis; however, the results should be viewed in the context of the limitations described above (Table 3, 4, Figure 6). The change in the AVNERP only reached statistical significance at 15 mcg/kg/min and 20 mcg/kg/min.

Although there was no significant decrease in the AERP from baseline up to 15 mcg/kg/min of dobutamine, there was a significant decrease in the AERP from baseline to 20 mcg/kg/min (Tables 2, 3, 4, Figure 6). However, the shortening of the AERP was likely due to shortening of the drive cycle length necessary to avoid competition with the shortening of the SCL. Although there was no significant decrease in the VERP from baseline to 5 mcg/kg/min of dobutamine, there was a significant decrease in the VERP from baseline to 10 mcg/kg/min, to 15 mcg/kg/min and to 20 mcg/kg/min dobutamine (Tables 2, 3, 4, Figure 6). The decrease in the VERP was likely secondary to the necessity of having to decrease the drive train cycle length due to the decrease in SCL with each dose escalation of dobutamine dose.

Changes in diastolic and systolic blood pressure with escalating doses of dobutamine are shown in Tables 2, 3, 4 and Figure 7. The systolic blood pressure increased significantly by 11 mm of Hg to a maximum at 15 mcg/kg/min and then decreased slightly at 20 mcg/kg/min. The diastolic blood pressure decreased significantly by 8 mm Hg to a minimum at 20 mcg/kg/min.

Three patients had no retrograde conduction at baseline. One patient developed retrograde conduction at 5 mcg/kg/min of dobutamine, one patient at 20 mcg/kg/min, and one patient had no retrograde conduction during the study.

Four patients (10%) were hypotensive, defined as systolic blood pressure <90 mmHg, at baseline (87, 83, 86, and 84), secondary to the effects of sedation. All four patients were able to tolerate dobutamine with no limitations. Hypotensive episodes were recorded in two additional patients (5%), a total of six patients (15%), during the study but none required a vasopressor nor subsequently developed end organ damage as a result. Another patient (2.5%) received a vasopressor for systolic blood pressure in the 90s based on the discretion of the anesthesiologist during 15 mcg/kg/min of dobutamine infusion and the dobutamine dose was not increased to 20 mcg/kg/min. One patient (2.5%) developed junctional rhythm at 20 mcg/kg/min of dobutamine but remained normotensive.

One patient (2.5%) developed atrial fibrillation at 10 mcg/kg/min and another patient (2.5%) developed AVNRT at 15 mcg/kg/min. For both patients, dobutamine was held and subsequently tolerated ablation with no further adverse events.

We did not perform ventricular pacing for VABCL or VERP in 13 patients who underwent AF ablations given the length of the procedure and the effect of ventricular pacing on the blood pressure.

Discussion

Isoproterenol, a non-selective beta agonist, is commonly used during EPS for its effects on enhancing conduction and shortening refractoriness of the AV node, particularly in sedated patients.[5]However, the cost of isoproterenol increased exponentially following ownership changes in 2015 such that the wholesale acquisition cost (WAC) per milligram increased from $26.20 in 2012 to $1,790.11 in 2015.[6,7] The cost implications were significant given the increasing number of catheter ablations. An estimated 10,000 atrial fibrillation ablation procedures were performed in the United States in 1992. The number increased to approximately 50,000 in 2013 and is continuing to rise.[1,2] Healthcare systems and electrophysiologists have coped with the financial burden by rationing the use of isoproterenol. A study reported 40% reduction in the number of hospitalized patients treated with isoproterenol from 2012 to 2015.[7]

Another response to the cost increase was substituting isoproterenol with dobutamine. The cost of dobutamine has remained steady with the WAC per milligram of $17.78 in 2012 and $16.50 in 2015, and the number of patients treated with dobutamine increased during this time.[7] Isoproterenol is a potent β1-adrenergic agent associated with chronotropic and proarrhythmic responses. Dobutamine was synthesized in hopes of mitigating the side effects of isoproterenol. Removing the hydroxyl group from isoproterenol led to the discovery of dobutamine, which has two isomers.[8] The S(-)-enantiomer dobutamine is a potent α1-adrenoceptor

agonist with minor β1 and β2-adrenoceptor agonist activities. In contrast, the R(+)-enantiomer dobutamine possesses minimal α1-agonist effects with predominantly β1 and β2-adrenoceptor agonist activities. The net effect of dobutamine is mostly β1-activity with mild β2 and α1-agonist effects. In addition, α1-activity helps offset β2-activity thus mitigating vasodilation-mediated hypotension, which is reported with high-doses of isoproterenol.[9]

Dobutamine is commonly used for cardiac stress imaging studies to assess the severity of coronary artery disease and its utilization has been well-studied.[10] Dobutamine stress echocardiography (DSE) was introduced as an alternative method for patients who cannot tolerate exercise, to provoke myocardial ischemia, leading to ST-segment changes on the ECG and regional wall motion abnormalities on two-dimensional echocardiography.[11] While dobutamine has a half-life of 2 minutes and may take up to 10 minutes to achieve a steady state, DSE is routinely performed with 3 minute intervals of dose increase, derived from the standard exercise Bruce protocol. There is no evidence to support this protocol, but the dose increase before reaching steady state has been largely adopted for safety concerns.[11] We used a hybrid approach in our study and started with 5 mcg/kg/min at increments of 5 mcg/kg/min up to 20 mcg/kg/min for five minutes each.

Buxton et al. studied the site-specific effects of isoproterenol at varying doses, and we conducted our study in a similar manner with dobutamine. Isoproterenol decreased the sinus cycle length at each incremental dose with the largest drop from 0.007 to 0.014 mcg/kg/min.[5] Dobutamine also decreased the sinus cycle length significantly by 10 mcg/kg/min with the largest decrease from 5 to 10 mcg/kg/min. Interestingly, the largest decrease in the AVNBCL and the VABCL also occurred between 5 and 10 mcg/kg/min. Similar to isoproterenol, dobutamine decreased the AH interval significantly by 15 mcg/kg/min, but there was no significant change in the HV interval. The lack of significant effect on the His-Purkinje system was consistent with previously reported studies in both animals and humans.[5] In contrast to the effects of isoproterenol more notable in the AV node compared to the sinus node, our study showed no significant difference in changes in the SCL relative to the changes in the AVNBCL or the VABCL over time with dose escalation. The AVNERP was often less than or equal to the AERP and therefore unable to be measured. Three patients (7.5%) had no retrograde conduction at baseline but two demonstrated retrograde conduction with 5 and 20 mcg/kg/min, which suggests bidirectional conduction enhancement.

At 5 mcg/kg/min of dobutamine, the VABCL decreased by a significant degree, indicating that even at low doses, there can be a significant effect on retrograde conduction, thus theoretically facilitating induction of specific arrhythmias like AVNRT at relatively low doses. Isoproterenol had been shown to improve retrograde conduction through the AV conducting system, thus facilitating induction of AVNRT.[5]

The safety of the use of dobutamine was an important observation of our study. Mazeika et al. utilized the same increments of dobutamine at 5, 10, 15, and 20 mcg/kg/min for eight minutes each during DSE and reported that all adverse reactions were minimal and resolved within two minutes of discontinuing the dobutamine infusion. Notably, seven patients (14%) had dobutamine-induced symptomatic hypotension of which three had transient junctional rhythms.[12] In our study, four patients (10%) were hypotensive at baseline (SBP 87, 83, 86, and 84) and a total of six patients (15%) developed hypotension during the study. One patient (2.5%), who did not meet our definition of hypotension (SBP <90 mmHg), was preemptively given a vasopressor by the anesthesiologist during the dobutamine infusion of 15 mcg/kg/min and did not experience any adverse events. Another patient (2.5%) developed junctional rhythm during 20 mcg/kg/min of dobutamine infusion but remained normotensive and spontaneously recovered normal sinus rhythm.

Multiple studies have shown that even higher doses of dobutamine for prolonged duration causes low incidence of serious side effects.[11] Gianni et al. reported that two patients (4.2%) with significant history of myocardial ischemia experienced paradoxical hypotension during the high-dose dobutamine infusion and two other patients (4.2%) had hypertensive responses while on norepinephrine for anesthesia-induced hypotension. The incidence of atrial arrhythmias and outflow tract premature ventricular contractions with high-dose dobutamine was comparable to high-dose isoproterenol.[9] In our study, AF was induced in one patient (2.5%) at 10 mcg/kg/min and AVNRT was induced in one patient (2.5%) at 15 mcg/kg/min of dobutamine at which point the study protocol was terminated.

Limitations

This was a single center study with limited number of patients. Our protocol did not go beyond 20 mcg/kg/min of dobutamine and does not qualify as a high dose dobutamine study. Anesthesia was not uniformly given with either general anesthesia or conscious sedation, which may have had variable effects on the cardiac conduction. In addition, anti-arrhythmic and/or rate control agents were not uniformly held before the procedure as the decision was up to the electrophysiologist based on the individual patient. Selection of patients was not consecutive because it was not always feasible to perform the study protocol due to time constraints. Moreover, we did not perform a VABCL or VERP in 13 patients who underwent AF ablations given the length of the procedure and the effect of ventricular pacing on the blood pressure. There were other limited missing variables which the authors deemed insignificant. Exclusion of patients due to time constraints could possibly introduce bias and affect the study results, especially if we excluded patients when procedures were long. Safety is always the priority, and if patients were under anesthesia for a prolonged period, we did not want to extend the procedure and place the patient at greater risk. Therefore, the more complicated, sicker patients with more cardiac substrate and longer procedure times (those patients undergoing atrial fibrillation ablation) were either excluded or ventricular pacing was not performed. Patients included in this study underwent electrophysiologic testing for a variety of indications. The heterogeneity of indications must be considered when interpreting results.

Conclusions

There was no difference in the magnitude of decrease of the AVNBCL and VABCL relative to the magnitude in decrease of the SCL at each incremental dose of dobutamine. However, the AVNBCL, the VABCL and the SCL decreased significantly from baseline with each incremental dose of dobutamine (except the 3% decrease in SCL from baseline to 5 mcg/kg/min dobutamine was not statistically significant). Dobutamine was also seen to enhance retrograde AV nodal conduction in two out of three patients who displayed no retrograde conduction at baseline. While hypotension and arrhythmia-inductions were noted, no significant hypertensive nor further adverse events were noted, which deems dobutamine a safe alternative to isoproterenol for EPS.

Other Members of the Dobutamine Study Group:

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References

1. Zipes DP, DiMarco JP, Jackman WM, et al. ACC/AHA Task Force Report: Guidelines for Clinical Intracardiac Electrophysiological and Catheter Ablation Procedures. J Am Coll Cardiol. 1995;26(2):555-573.
2. D'Silva A, Wright M. Advances in imaging for atrial fibrillation ablation. Radiol Res Pract. 2011;2011:714864.
3. Tuttle RR, Mills J. Dobutamine: development of a new catecholamine to selectively increase cardiac contractility. Circ Res. 1975; 36(1):185-196.
4. Vanegas DI, Perez C de J, Montenegro J de J, et al. Dobutamine use for arrhythmia induction during electrical programmed heart stimulation. Rev Colomb Cardiol. 2006;12(7):479-483.
5. Cossú SF, Rothman SA, Chmielewski IL, Hsia HH, Vogel RL, Miller JM, Buxton AE. The effects of isoproterenol on the cardiac conduction system: site-specific dose dependence. J Cardiovasc Electrophysiol. 1997 Aug;8(8):847-53. doi: 10.1111/j.1540-8167.1997.tb00845.x. PMID: 9261710.
6. Knight BP. The rising costs of isoproterenol. EP Lab Dig. 2013 Mar;17(3).
7. Khot UN, Vogan ED, Militello MA. Nitroprusside and Isoproterenol Use after Major Price Increases. N Engl J Med. 2017 Aug 10;377(6):594-595. doi: 10.1056/NEJMc1700244. PMID: 28792879.
8. Cismaru G. Arrhythmia induction in the EP lab. 1st ed. Cham, Switzerland: Springer Nature Switzerland AG;2019:71-86.
9. Gianni C, Sanchez JE, Mohanty S, Trivedi C, Della Rocca DG, Al-Ahmad A, Burkhardt JD, Gallinghouse GJ, Hranitzky PM, Horton RP, Di Biase L, Natale A. High-Dose Dobutamine for Inducibility of Atrial Arrhythmias During Atrial Fibrillation Ablation. JACC Clin Electrophysiol. 2020 Dec

14;6(13):1701-1710. doi: 10.1016/j.jacep.2020.07.018. Epub 2020 Sep 30. PMID: 33334450.
10. Piérard LA, Berthe C, Albert A, Carlier J, Kulbertus HE. Haemodynamic alterations during ischaemia induced by dobutamine stress testing. Eur Heart J. 1989 Sep;10(9):783-90. doi: 10.1093/oxfordjournals.eurheartj.a059571. PMID: 2806276.
11. Lu D, Greenberg MD, Little R, Malik Q, Fernicola DJ, Weissman NJ. Accelerated dobutamine stress testing: safety and feasibility in patients with known or suspected coronary artery disease. Clin Cardiol. 2001 Feb;24(2):141-5. doi: 10.1002/clc.4960240208. PMID: 11214744; PMCID: PMC6654775.
12. Mazeika PK, Nadazdin A, Oakley CM. Dobutamine stress echocardiography for detection and assessment of coronary artery disease. J Am Coll Cardiol. 1992 May;19(6):1203-11. doi: 10.1016/0735-1097(92)90325-h. PMID: 1564221.
13. Burger AJ, Notarianni MP, Aronson D. Safety and efficacy of an accelerated dobutamine stress echocardiography protocol in the evaluation of coronary artery disease. Am J Cardiol. 2000 Oct 15;86(8):825-9. doi: 10.1016/s0002-9149(00)01100-0. PMID: 11024395.
14. Masoni A, Alboni P, Malacarne C, Codeca L. Effects of dobutamine on electrophysiological properties of the specialized conduction system in man. J Electrocardiol. 1979 Oct;12(4):361-70. doi: 10.1016/s0022-0736(79)80004-7. PMID: 512532.
15. Hariman, Robert J, Gomes, Joseph, El-Sharif, N. Catecholamine-dependent Atrioventricular Nodal Reentrant Tachycardia. Circulation 1983;67(3):1983.

Figure Legends.

Figure 1. Demonstrates the relative decrease in sinus cycle length from baseline to 5 mcg/kg/min, 10 mcg/kg/min, 15 mcg/kg/min and 20 mcg/kg/min of dobutamine.

Figure 2. Demonstrates the relative decrease in AVNBCL and VABCL from baseline to 5 mcg/kg/min, 10 mcg/kg/min, 15 mcg/kg/min and 20 mcg/kg/min of dobutamine.

Figure 3. Demonstrates the relative decrease in AH interval from baseline to 5 mcg/kg/min, 10 mcg/kg/min, 15 mcg/kg/min and 20 mcg/kg/min of dobutamine.

Figure 4. Demonstrates the relative change in HV interval from baseline to 5 mcg/kg/min, 10 mcg/kg/min, 15 mcg/kg/min and 20 mcg/kg/min of dobutamine.

Figure 5. Demonstrates the relative change in QRS duration and QT interval from baseline to 5 mcg/kg/min, 10 mcg/kg/min, 15 mcg/kg/min and 20 mcg/kg/min of dobutamine.

Figure 6. Demonstrates the relative change in AERP, AVNERP and VERP from baseline to 5 mcg/kg/min, 10 mcg/kg/min, 15 mcg/kg/min and 20 mcg/kg/min of dobutamine.

Figure 7. Demonstrates the relative change in diastolic blood pressure and systolic blood pressure from baseline to 5 mcg/kg/min, 10 mcg/kg/min, 15 mcg/kg/min and 20 mcg/kg/min of dobutamine.

Table 1. Patient Demographics and EP/Ablation Indications

Patient Demographics

Age (years)	63 (55-83)
Female Sex	11 (28)
Body Mass Index kg/m^2	29 (26-35)
Hypertension	30 (75)
Hyperlipidemia	21 (53)
Coronary Artery Disease	5 (13)
Atrial Fibrillation	23 (58)
Diabetes Mellitus	8 (20)
Anticoagulation	23 (58)
Rate-Control Agents	28 (70)

Rhythm-Control Agents	9 (23)
Ejection Fraction (%)	61 (45-65)
EP/Ablation Procedure Indications	EP/Ablation Procedure Indications
Atrial Fibrillation	18 (45%)
Atrial Flutter	11 (28%)
Atrial Tachycardia	6 (15%)
Atrial Ventricular Node Reentry Tachycardia	6 (15%)
Premature Ventricular Contraction	2 (5%)
Electrophysiology Study	2 (5%)

Values are median (25^{th}-75^{th}percentiles) and frequency (percentage)

Table 2: Measured Electrophysiologic Parameters with Incremental Dobutamine Dosing

	Baseline	5 mcg/kg/min	10 mcg/kg/min	15 mcg/kg/min	20 mcg/kg/min
SCL	909 (793, 1056)	850 (761, 1080)	801 (600, 899)	618 (545, 744)	556 (496, 701)
AVNBCL	360 (320, 430)	360 (305, 385)	305 (270, 370)	280 (250, 320)	250 (230, 300)
VABCL	455 (360,600)	420 (330, 530)	340 (280, 480)	300 (250, 390)	290 (260, 360)
AH interval	74 (64, 99)	71 (61, 87)	71 (58, 86)	62 (55, 71)	58 (51, 70)
HV interval	50 (43, 54)	47 (42, 56)	48 (41, 52)	47 (41, 53)	47 (41, 54)
QT	411 (366, 451)	414 (380, 450)	394 (365, 427)	377 (344, 418)	362 (319, 393)
AVNERP	320 (260, 370)	290 (250, 320)	260 (220, 310)	230 (190, 300)	220 (200, 290)
QRS duration	95 (83, 105)	93 (80, 104)	90 (82, 104)	93 (84, 102)	88 (78, 100)
AERP	230 (200, 260)	225 (200, 250)	210 (190, 240)	200 (180, 240)	190 (165, 220)
VERP	260 (235, 290)	240 (220, 280)	240 (200, 260)	210 (200, 250)	220 (190, 240)
SBP	112 (99, 124)	111 (104, 119)	118 (108, 126)	124 (107, 136)	117 (100, 135)
DBP	65 (58, 72)	64 (58, 70)	62 (56, 68)	60 (54, 69)	59 (53, 65)

Values are Median (25^{th}-75^{th}percentile). All values are in msec.

Table 3: Percent Change from Baseline in Measured Electrophysiologic Parameter with Incremental Dobutamine Dosing

	5 mcg/kg/min	10 mcg/kg/min	15 mcg/kg/min	20 mcg/kg/min
SCL	-4 (-11, 0)	-20 (-30, -6)	-30 (-39, -17)	-35 (-43, -23)
AVNBCL	-5 (-11, 0)	-16 (-29, -9)	-24 (-33, -16)	-29 (-36, -22)
VABCL	-7 (-16, 0)	-19 (-27, -8)	-30 (-36, -23)	-32 (-38, -22)
AH interval	-5 (-14, 2)	-8 (-19, 4)	-13 (-23, -5)	-18 (-27, -11)
HV interval	-2 (-8, 7)	-5 (-12, 12)	-5 (-15, 12)	0 (-15, 12)
QT interval	0 (-4, 8)	-3 (-7, 3)	-9 (-16, 1)	-12 (-18, -5)
AVNERP	-7 (-17, 0)	-8 (-29, 0)	-29 (-41, -11)	-33 (-42, -9)
QRS Duration	-1 (-9, 4)	-1 (-7, 5)	-3 (-8, 4)	-5 (-12, 3)
AERP	-4 (-9, 0)	0 (-13, 0)	-5 (-15, 0)	-13 (-20, -5)
VERP	-4 (-8, 0)	-8 (-17, -3)	-14 (-22, -8)	-15 (-23, -9)
SBP	0 (-6, 5)	6 (-2, 15)	3 (-4, 25)	5 (-7, 19)
DBP	-4 (-8, 6)	-4 (-14, 2)	-8 (-19, 3)	-11 (-18, 2)

Values are % change (25^{th}-75^{th}percentile).

Table 4. Percent Change from Baseline of Individual Parameters by Dobutamine Dose

Dose	SCL	AVNBCL	VABCL	AH	HV	QRS
5	-3 (-10, 4)	-6 (-11, -1)*	-9 (-15, -3)	-5 (-12, 3)	-2 (-9, 6)	-2 (-7, 4)
10	-19 (-27, -12)*	-18 (-23, -13)*	-20 (-26, -14)	-8 (-16, 0)	-2 (-10, 6)	-2 (-8, 4)
15	-28 (-36, -21)*	-25 (-30, -20)*	-30 (-36, -24)	-14 (-21, -6)*	-1 (-9, 7)	-1 (-7, 4)
20	-32 (-40, -25)*	-29 (-34, -24)*	-31 (-37, -25)	-18 (-26, -11)*	0 (-8, 8)	-5 (-11, 1)

Values are % change. Values in parenthesis are 99% confidence intervals. *P $<$ 0.01

Dose	QT	AVNERP	AERP	VERP	SBP	DBP
5	2 (-2, 6)	-10 (-23, -2)*	-5 (-14, 5)	-5 (-10, 1)	3 (-5, 11)	-1 (-8, 6)
10	-4 (-8, 0)*	-11 (-25, -4)*	-3 (-13, 6)	-12 (-17, -6)*	7 (-2, 15)	-3 (-10, 4)
15	-8 (-12, -4)*	-27 (-42, -12)*	-8 (-17, 2)	-16 (-21, -10)*	11 (3, 20)*	-5 (-12, 2)
20	-12 (-16, -8)*	-28 (-44, -12)*	-14 (-24, -4)*	-16 (-22, -11)*	7 (-2, 15)	-8 (-15, 0)*

Values are % change. Values in parenthesis are 99% confidence intervals. *P $<$ 0.01

Figure 1. Change in Sinus Cycle Length with Incremental Dobutamine Dosing

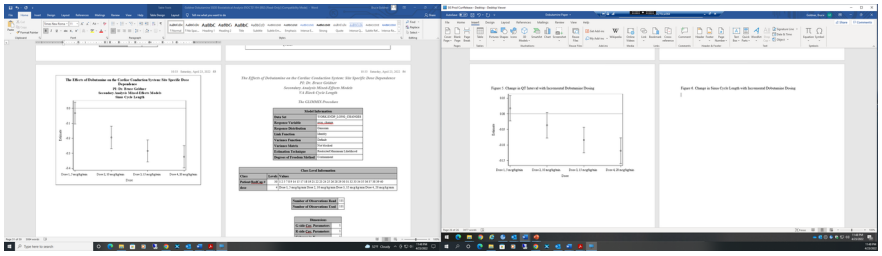

Figure 2. Change in AVNBCL and VABCL with Incremental Dobutamine Dosing

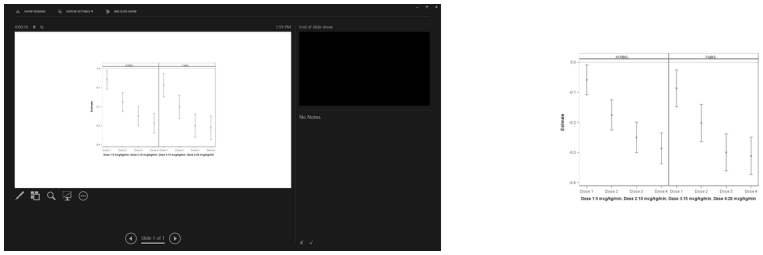

Figure 3. Changes in AH Interval with Incremental Dobutamine Dosing

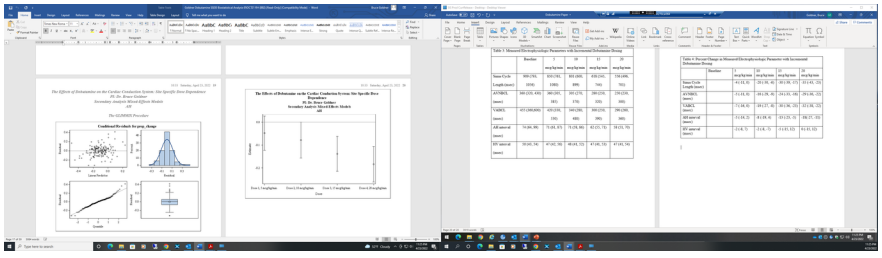

Figure 4. Change in HV with Incremental Dobutamine Dosing

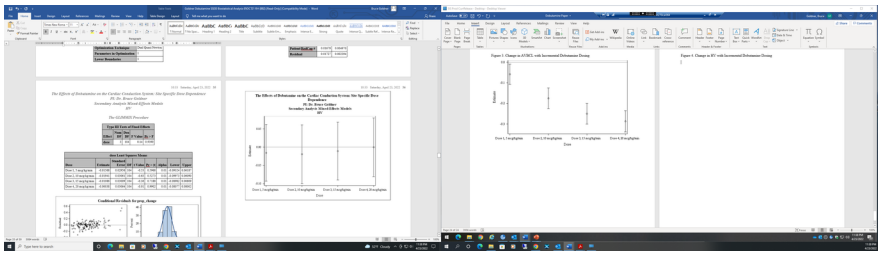

Figure 5. Change in QRS Duration and QT with Incremental Dobutamine Dosing

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Figure 6. Change in AERP, AVNERP and VERP with Incremental Dobutamine Dosing.

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Figure 7. Change in Diastolic Blood Pressure and Systolic Blood Pressure with Incremental Dobutamine Dosing

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