Determining the Optimal Dose of Adenosine for Unmasking Dormant Pulmonary Vein
Conduction Following Atrial Fibrillation Ablation: Electrophysiological and Hemodynamic
Assessment. DORMANT-AF study

Short Title

The DORMANT-AF study

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/jce.13107](https://doi.org/10.1111/jce.13107).

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Drs. Sandeep Prabhu, Ling-han Ling, Alexandr Voskoboinik, Geoff Lee, Chrishan J Nalliah, and Bupesh Pathik receive funding from Australian National Health and Medical Research Council (NHMRC) and/or National Heart Foundation of Australia. Dr. Geoff R Wong receives funding from the Cardiac Society of Australia and New Zealand. Drs Sandeep Prabhu and Alexandr Voskoboinik also receive funding from the Baker IDI Heart and Diabetes Research Institute.

Professor JM Kalman is in part supported by the NHMRC. Professor M Kistler is supported by practitioner fellowships from the NHMRC. This research is supported in part by the Victorian Government's Operational Infrastructure Funding.

Dr. Kalman reports participation on research grants from Medtronic, Biosense Webster, St. Jude Medical & Boston Scientific; speaker's bureau compensation from Medtronic & Boston Scientific; serving on advisory boards of Biosense Webster & Boston Scientific. Other authors: No disclosures.

Abbreviations

AF	atrial fibrillation
ATP	adenosine triphosphate
AVB	atrio-ventricular block
BMI	body mass index
DM	diabetes mellitus
IBW	ideal body weight
LA	left atrium
MBP	mean blood pressure
PV	pulmonary vein
PVI	pulmonary vein isolation

SBP systolic blood pressure

WACA wide antral circumferential ablation

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Abstract

Introduction

The significance of adenosine induced dormant pulmonary vein (PV) conduction in AF ablation remains controversial. The optimal dose of adenosine to determine dormant PV conduction is yet to be systematically explored.

Methods and Results

Consecutive patients undergoing index AF ablation received 3 adenosine doses (12mg, 18mg, 24mg) in a randomized blinded order, immediately after PVI. Electrophysiological (PR prolongation, AV block (AVB) and PV reconnection) and hemodynamic (BP) parameters were measured. 339 doses (113/dose) assessed 191 PVs in 50 patients (66% male, 72% PAF, 52% hypertensive). Dormant PV conduction occurred in 28% of patients (16.5% (32) of PVs). All cases were associated with AVB (AVB: PV reconnection vs. no PV reconnection 100% vs. 83%, $p=0.007$). AVB occurred more frequently at 24mg vs. 12mg (92% vs. 82%, $p=0.019$) but not vs. 18mg (91%, $p=0.62$). AVB duration progressed between 12mg ($12.0 \pm 8.9s$), 18mg ($16.1 \pm 9.1s$, $p=0.001$) and 24mg ($19.0 \pm 9.3s$, $p<0.001$) doses. MBP fell further at 24mg (ΔMBP : $27 \pm 12mmHg$) and 18mg ($26 \pm 13mmHg$) dose compared to 12mg ($22 \pm 10mmHg$ vs., $p<0.001$). A significant reduction in AVB in patients $> 110kg$ (65% vs. 91% in 70-110kg group, $p<0.001$) in response to adenosine was seen.

Conclusion

An adenosine dose producing AVB is required to unmask dormant PV conduction. AVB is significantly reduced in patients > 110kgs. Weight and dosing variability may in part explain the conflicting results of studies evaluating the clinical utility of adenosine in PVI.

Keywords

adenosine

atrial fibrillation

catheter ablation

dormant conduction

atrioventricular block

hemodynamic

Introduction

Durable pulmonary vein isolation remains the cornerstone of AF ablation^{1, 2}. There has been much interest in the role of adenosine in identifying dormant PV/LA conduction following acute pulmonary vein isolation (PVI), and its implications for long-term clinical outcome^{3, 4}. However recent single-center and large multicenter trials have reported conflicting results⁵⁻⁷. The confusion surrounding the role of adenosine may be in part explained by variation in adenosine dosing strategies and dosing endpoints among published studies⁸⁻¹². Given the unique pharmacokinetics of adenosine, in particular an ultra-short half-life, dosing is likely to have a significant impact on its usefulness. Nonetheless, a systematic characterization of the electrophysiological and hemodynamic effects of adenosine has not been previously explored. We sought to undertake a comprehensive prospective dose finding study to determine: (1) the dose response relationship of adenosine and pulmonary vein reconnection, (2) the relationship between electrophysiological and hemodynamic indicators of adenosine activity and PV reconnection, and (3) establish practical dosing guidelines for the use of adenosine in PVI.

Methods

Patient selection

This multicenter study enrolled consecutive patients undergoing index AF ablation from July 2015 to February 2016. Exclusion criteria consisted of: (1) refusal to consent to study; (2) a

history or severe or poorly controlled airway disease; (3) pre-existing complete heart block; (4) known hypersensitivity to adenosine; (5) severe valvular stenosis; or (6) untreated or un-evaluated coronary artery disease. The study protocol and design were approved by the local ethics committee at each of the centers involved in the trial.

Catheter ablation procedure

Oral anticoagulation was discontinued 24-48hrs pre-procedure with the exception of vitamin K antagonists, which were continued. Antiarrhythmic medication was discontinued 5 half-lives pre-procedure with the exception of amiodarone. All procedures were performed under general anaesthesia with the assistance of a 3D mapping system (NAVX, St Jude Medical). After exclusion of intra-cardiac thrombosis, a deca and quad polar catheter were positioned in the coronary sinus and HIS position, respectively. Transesophageal echocardiographic guided double transseptal punctures were performed (SL1 8 and 8.5F sheaths). Unfractionated heparin was administered to achieve an activated clotting time of >350 seconds. Mapping of the left atrium and pulmonary veins (PVs) was performed with a 20 pole spiral catheter, and ablation with a 4mm irrigated-tipped catheter (Flexibility D/F, St Jude Medical). Bidirectional PVI was the endpoint in all procedures and was achieved with wide antral circumferential ablation (WACA) with addition ablation within the WACA to achieve isolation if required. Additional ablation lines or substrate modification were performed at operator discretion.

Adenosine dosing protocol

Electrophysiologic and hemodynamic response to three different doses of adenosine (12, 18 and 24mg) was assessed. Adenosine challenge was performed during CS pacing at 600ms

following acute PVI. If the superior and inferior veins isolated en bloc, then the superior and inferior veins were tested simultaneously with adenosine. The ablation catheter was always used in concert with the multipolar catheter in the opposing vein to assess dormant conduction during adenosine challenge if:

1. the upper and lower veins isolated en bloc and as such were electrically connected to each other and
2. no ablation was performed on the intervenous ridge.

Otherwise, the veins were individually assessed with multipolar catheter in each upper and lower vein with each vein tested separately with all three doses. The multipolar catheter and ablation catheter, where utilized, were positioned at the pulmonary venous ostium as determined by 3D mapping and local PV electrograms. Each dose of adenosine was diluted with normal saline to 10mL volume and administered in a random order as determined by a computer algorithm (random.org random sequence generator). The primary operator, anesthetist and technician were blinded to the dose order, which was administered sequentially following the intervening complete recovery of conduction and blood pressure (approximately 2-4 minutes). Each dose was administered in a standardized manner via a cubital 18-20 gauge intravenous canula in the forearm as a rapid bolus injection (recorded as 'time zero' in the log), immediately followed by a 10mL rapid saline flush. In the event of adenosine mediated PV reconnection, all 3 doses were completed then further ablation performed and the veins retested with each adenosine dose in the original manner. Ablation was completed with the endpoint of no further dormant conduction.

Pulmonary vein reconnection

Adenosine mediated PV dormant conduction was defined as the transient appearance of associated PV signals in the multipolar and or ablation catheter occurring within 2 minutes following adenosine administration. Spontaneous reconnection was defined as the occurrence of PV/LA reconnection in the absence of adenosine activity.

Hemodynamic measurements

All patients had general anesthesia and continuous blood pressure monitoring via a radial arterial pressure line. Hemodynamic support was standardized with a metaraminol or phenylephrine infusion aiming for baseline SBP > 100mmHg prior to adenosine administration; additional boluses could be administered at the anesthetist's discretion. The following hemodynamic parameters were recorded:

1. Baseline blood pressure (BP): BP recorded immediately prior to administration of each adenosine dose.
2. Nadir BP: the lowest BP recording after administration of each adenosine dose following the return of 1:1 atrioventricular conduction (to avoid the confounding effect on systemic BP of low cardiac output in the setting of adenosine induced transient AVB).
3. Time to nadir BP: the time from time zero to the nadir BP

Electrophysiologic measurements

Electrograms were continuously recorded utilizing EP WorkMate (St Jude Medical) or CardioLab (General Electric). All intervals were measured offline using inbuilt horizontal electronic callipers. For each adenosine dose, the following measurements were recorded:

1. Time zero time point at which the adenosine dose was administered.

2. Baseline PR interval just prior to time zero.
3. Interval from time zero to the p wave onset of the first beat with PR prolongation > 20ms from baseline. This approximates the time from administration to initial onset of adenosine activity.
4. Interval from time zero to the onset of the first non-conducted p wave. This approximated the time from adenosine administration to full adenosine activity.
5. Interval from the onset of the first non-conducted p waves to the onset of the first conducted p wave. This approximates the duration of maximal adenosine activity.
6. The interval from the onset of the first beat with PR prolongation >20ms to the onset of the first p wave with baseline PR interval (i.e., PR interval recovery). This approximates the total time of adenosine activity.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation (SD) unless otherwise indicated. After assessment of normal distribution with the Kolmogorov–Smirnov test, two-group comparisons were made using Student's t test for continuous variables, or the Chi-squared test for categorical variables. A two-tailed p value of <0.05 was considered significant. Correlation was determined by using the Pearson Product-Moment correlation coefficient and a linear regression model. Analyses were conducted using SPSS software (version 23, IBM, Chicago, Illinois).

Results

Study Population (Table 1 and 2)

Fifty-five consecutive patients undergoing AF ablation at 2 centers were screened. Five were excluded, 3 due to the presence of significant airway disease, 1 patient with significant baseline hypotension and 1 patient refused to consent. Fifty patients were subsequently included in the analysis. Their baseline demographic and procedural details are listed in Table 1. Patients were predominately male (66%), hypertensive (52%) with paroxysmal AF (72%) and an average CHADS₂ score 1.3 ± 1.0 . Average LVEF was normal ($58.9 \pm 6.7\%$) with mild LA enlargement (LA area: $24.6 \pm 6.9\text{cm}^2$, LA diameter $4.2 \pm 0.8\text{cm}$). Nine (18%) patients had 3-vein anatomy with a left common PV in all cases, the remainder having 4 pulmonary veins. Pulmonary vein isolation was achieved in all (100%) patients, with 12 patients (24%) receiving further substrate modification involving posterior LA isolation. Overall, 339 adenosine doses (113 at each dose) were administered assessing 191 individual PVs with 585 individual vein challenges.

Pulmonary vein reconnection (Figure 1)

Pulmonary vein reconnection occurred in 28% (14 patients) and 16.5% (32) of pulmonary veins assessed. This represented 35 individual doses, and 63 individual vein challenges. All cases (100%) of PV reconnection were associated with transient AVB with at least one non-conducted atrial paced beat (100% vs. 83%, $p=0.007$). There were no instances of dormant conduction in the absence of AV block. In those veins demonstrating dormant conduction (16%), no dormant conduction was evident in those veins at adenosine doses insufficient to produce AV block. The presence of dormant PV conduction predicted the subsequent occurrence of spontaneous PV reconnection (Table 2). In this study, all cases of spontaneous PV reconnection following adenosine mediated reconnection persisted in the setting of adenosine mediated reconnection. Such cases were interpreted as having both adenosine mediated and

spontaneous reconnection (33%) and accounted for much of the predictive relationship demonstrated in this study (see table). Spontaneous PV reconnection occurred in 11% of PVs in the absence of adenosine mediated reconnection ($p=0.004$, OR=4.22, 95%CI: 1.51-11.83). Additional RF was applied at the site of PV reconnection and adenosine at all 3 doses repeated to confirm electrical isolation. There were no instances of spontaneous reconnection following the application of further ablation for adenosine-mediated reconnection.

There were significantly longer procedure times (dormant conduction vs no dormant conduction: 190 ± 30 vs 160 ± 36 mins, $p=0.01$) and longer RF times (48 ± 9.8 vs 42 ± 8.5 mins, $p=0.024$) in patients with dormant conduction compared to those without dormant conduction.

Electrophysiological Parameters (Table 4)

The electrophysiological markers of adenosine activity at each adenosine dose (339 in total, 113 challenges at each dose) were assessed and are summarized in Table 3. There was no difference in time from administration to the onset of adenosine activity (time to PR prolongation or AV block) between the doses. AVB was more likely to occur at 24mg compared to 12mg of adenosine (92% vs. 82%, $p=0.019$) but no more likely than 18mg (91%, $p=0.62$). Similarly, the duration of adenosine cardiac activity (the time from PR prolongation to PR recovery) differed significantly between the 24mg and 12mg doses (35.4 ± 10.7 s vs. 28.6 ± 11.2 secs, $p<0.001$), but not between the 24 and 18mg doses (33.1 ± 11.8 secs, $p=0.15$). There was a significant increase in the duration of AVB with 12mg (12.0 ± 8.9 secs) vs. 18mg (16.1 ± 9.1 s, $p=0.001$) vs. 24mg of adenosine (19.0 ± 9.3 s, $p<0.001$).

Given the requirement for adenosine induced AVB to unmask dormant PV conduction, the dose per kg (both actual and ideal body weight) of adenosine was correlated with the duration of

AVB (Figure 2). A significant linear relationship between dose/kg and duration of AVB was demonstrated ($R=0.51$, $p<0.001$). Doses above 0.3mg/kg were 100% sensitive in achieving AV block.

Hemodynamic Parameters (Table 5)

Baseline blood pressure was comparable prior to each dose and there was no difference on time to blood pressure nadir between the doses. Both the absolute magnitude and percentage of average mean blood pressure drop was significantly greater in the 24mg and 18mg compared to the 12mg doses (Δ MBP; 12 vs. 24mg: -22 ± 10 vs. -27 ± 12 mmHg, $p<0.001$; 12 vs. 18mg, -26 ± 13 mmHg vs. -41) with a ceiling effect between the 18 and 24mg doses ($p=0.21$, $p=0.34$). There was no difference in blood pressure response between doses responsible for dormant PV conduction and those that did not ($p=0.71$).

Body Weight and Adenosine dose (Figure 3)

To assess the impact of body weight upon measured electrophysiological and hemodynamic parameters, the study population was stratified according to body weight; adenosine doses in patients weighing ≥ 90 kg ($n=144$) demonstrated a significantly attenuated response. There was a significant reduction in the occurrence of AV block (92% vs. 82%, $p=0.009$), duration of AVB (12.98 ± 8.76 vs. 17.56 ± 9.71 s, $p<0.001$) and duration of adenosine cardiac activity (28.4 ± 9.9 vs. 35.10 ± 11.8 s, $p<0.001$) across all adenosine doses compared with patients <90 kg ($n=195$). In addition, the time to onset of adenosine activity (PR prolongation, $p=0.007$ and AV block onset, $p=0.011$) was also reduced (see Table 4). Significant differences in the duration of AVB and duration of adenosine cardiac activity were demonstrable at each individual dose (12mg:

p=0.0052, p=0.0046; 18mg: p=0.0073, p=0.0041; 24mg: p=0.041, p=0.0095). Similarly, an attenuated hemodynamic response to doses in patients ≥ 90 kg was also noted (Δ MBP: ≥ 90 kg vs. < 90 kg: -21 ± 8.3 vs. -29 ± 13 mmHg, $p < 0.001$).

Patients were further stratified into four groups (< 70 kg, 70-90kg, 91-110kg and > 110 kg). There were no significant differences between the 70-90kg and 91-110kg groups with respect to both electrophysiological and hemodynamic parameters (70-90kg vs. 91-110kg: AVB: 91% vs. 91%, $p = 1.0$; duration of AVB: 14.0 vs. 14.6s, $p = 0.60$; mean percentage drop in MBP: 33.7% vs. -35.6%, $p = 0.22$). Hence patients in these groups were combined and the doses were compared between three groups (< 70 kg, 70-110kg and > 110 kg). There was a significant reduction in the incidence of AVB in patients > 110 kg (65% vs. 91% in 70-110kg group; $p < 0.001$; and 97% in weight < 70 kg, $p < 0.001$), and in the duration of AVB when present (> 110 kg 10.1seconds vs. 14.3s in 70-110kg group, $p = 0.006$; vs. < 70 kg: 10.1s vs. 23.8s, $p < 0.001$). Hemodynamic effects (average percentage drop in MBP from baseline) were attenuated in patients > 110 kg (24.5% vs. 34.9% in 70-110kg, $p < 0.001$; vs. 43.8% in < 70 kg, $p < 0.001$). Notably, the ceiling effect with respect to electrophysiological and hemodynamic parameters observed with doses above 18mg described above was not demonstrable when patients > 110 kg were considered in isolation. The distribution of weights across the study population, with the highest number in the 70-110kg group (66%), likely explains the apparent 'ceiling' effect of doses, when the cohort was analyzed as a whole. Practical guidance for adenosine dose selection, incorporating weight variability, is provided in figure 4.

Discussion

The present study provides a: (1) systematic evaluation of the effect of varying adenosine doses on the ability to unmask dormant pulmonary vein conduction following acute pulmonary vein

isolation; (2) characterize the relationship between the electrophysiological and hemodynamic effects of adenosine and dormant PV conduction. The major findings from the present study are:

1. Adenosine mediated dormant pulmonary vein conduction was only demonstrated at doses sufficient to demonstrate AVB with at least one non-conducted atrial paced beat;
2. Other than the requirement to achieve AVB, there is no demonstrable relationship between dormant conduction and varying doses of adenosine;
3. The presence of dormant PV conduction following acute pulmonary vein isolation is predictive of spontaneous PV reconnection (11% vs. 3% of doses, $p=0.014$; OR=4.34, 95%CI: 1.21-14.53);
4. In patients < 110kg, there was no advantage in adenosine doses beyond 18mg with a ceiling effect upon electrophysiological and hemodynamic markers of adenosine activity demonstrated.
5. In patients > 110kg there was relative resistance to adenosine with AV block not achieved in 35%.

The practical implications are that if adenosine is being utilized to determine dormant PV conduction following PVI it must be administered in a dose sufficient to cause AVB with at least one non-conducted atrial paced beat. On the basis of the present study the following dose based on weight are recommended:

- Patients < 70kg - adenosine minimum 12mg
- Patients 70-110kg - adenosine minimum 18mg
- Patients >110kg – adenosine 24mg or higher aiming for dose >0.3mg/kg.

- Repeat adenosine at higher dose if AVB not achieved

The Mechanism of Adenosine in AF ablation

The present study demonstrates the importance of sufficient adenosine to achieve AVB as required to illicit dormant PV conduction. Datino and colleagues elegantly characterized the mechanism of adenosine in unmasking dormant conduction in the canine model. Adenosine hyperpolarizes vulnerable atrial myocytes via potassium channels (I_{KAdo}), which restores voltage-dependent sodium channels (I_{Na}), facilitating electrical conduction and results in transient PV/LA reconnection¹³. However, conduction slowing and AV block is the result of adenosine mediated effects on I_{KAdo} channels and an inhibition of L-type calcium channels (I_{CaL})¹⁴. Provided AVB was achieved, there was no observable benefit to higher doses in the identification of dormant conduction.

Clinical Implications

Dosing regimens in trials evaluating adenosine mediated dormant conduction, including the two largest randomized trials, have varied considerably¹⁵⁻¹⁸. However, the potential impact of adenosine dosing upon the clinical outcomes has not been explored. Macle and colleagues performed a multicenter randomized controlled trial involving 534 patients with paroxysmal AF with dormant conduction present in 284 (53%). Patients randomized to further ablation had a significant improvement in freedom from AF (69%) compared to those randomized to no further ablation (42%). Importantly, Macle et al utilized adenosine at a minimum dose of 12mg, which was then titrated to achieve at least one blocked p wave or a sinus pause of > 3 second⁶. In contrast, Kobori et al recruited 2,113 AF patients (33% with non-paroxysmal AF) and

randomized 1112 patients to adenosine-triphosphate (ATP) guided pulmonary vein isolation (with further ablation if dormant conduction identified) or no ATP. There was no significant difference in freedom from AF at 12 months between the groups⁵. A standard dose of 0.4mg/kg of ATP as a single rapid bolus was administered with no requirement for conduction slowing or AV block, and the incidence of AV block was not reported. The pharmacological characteristics of ATP and adenosine have been reviewed by Belhassen and colleagues¹⁹. Doses of 15-40mg of ATP were associated with transient sinus bradycardia or first or second-degree AVB, but not complete AV block. A rapidly infused dose of ATP at 0.3mg/kg in 48 healthy subjects demonstrated sinus bradycardia or conduction slowing in only 48% of patients. In contrast, doses of adenosine administered at doses of 0.18mg/kg in 17 subjects were able to achieve AVB in all cases.

ATP is completely metabolized to adenosine, which is responsible for the electrophysiological effect of ATP, which may explain its different pharmacological profile to adenosine, and a greater dependence on rate of infusion. Belhassen concluded that ATP possessed half the potency of adenosine at equivalent doses^{19, 20}. A dose of 0.4mg/kg of ATP, as utilized by Kobori and colleagues is likely equivalent to 0.2mg/kg of adenosine, at which AV block may not be reliably achieved. Hence, it is possible that a proportion of patients in the ATP guided PVI arm may have had dormant conduction undetected due to an inadequate ATP dose. This may have affected the ability of further ablation to improve outcome as a proportion of patients receiving no additional ablation may have had undetected dormant conduction. Our findings suggest that the varying dosing regimens may in part explain the contradictory results of these large multicenter trials.

Dormant PV conduction and spontaneous reconnection

In our study the occurrence of dormant PV conduction as performed immediately after achieving acute PVI was predictive of subsequent spontaneous reconnection. However, 3% of veins with no dormant conduction at any dose subsequently developed spontaneous reconnection over a 30-minute waiting time. This is reflective of differing physiological processes associated with reconnection in each situation. Arjuna et al evaluated 15 patients with cardiac MRI immediately following PVI and demonstrated that the ablation line consisted of both delayed enhancement, consistent with necrosis, and high T2 signal intensity, indicative of edema. Those with subsequent PV reconnection showed a higher proportion of high T2 signal relative to delayed enhancement, compared to those without PV reconnection²¹. This suggests that the mechanism of spontaneous PV reconnection may depend on the resolution of edema between neighboring regions of necrosis. In contrast, adenosine acts via I_{KAdo} in surviving functional myocytes to facilitate dormant conduction. The presence of dormant conduction following acute PVI may reflect both the absence of necrosis and edema. This finding is supported by Jiang et al who found that in patients with both adenosine mediated and spontaneous PV reconnection such reconnection appeared to occur via the same gap²². Das and colleagues recently demonstrated that further ablation at sites of acute reconnection may negate their culpability for sites of subsequent late reconnection²³. However, the pathologic mechanisms responsible for spontaneous and adenosine mediated PV reconnection may differ significantly as acute testing with adenosine does not replace a suitable waiting period for spontaneous recovery.

Dose Relationship to Electrophysiological and Hemodynamic Parameters

In the present study the electrophysiological and hemodynamic effects of adenosine displayed a plateau beyond doses above 18mg in patients less than 110kg (figure 4). This was evident with

respect to the occurrence of AVB, the duration of adenosine cardiac activity and the magnitude of blood pressure drop from baseline. This finding is important given the sole determinant for adenosine dose is that dose which reliably achieves AVB to demonstrate dormant PV conduction where it exists. Thus, the routine administration of adenosine doses above 18mg may generally not be required in patients less than 110kgs. In contrast, there was a relative resistance to adenosine in patients > 110kg with over a third of patients failing to achieve AVB. This finding is not unexpected given the near linear relationship between circulating blood volume and weight²⁴; however, its impact upon electrophysiological and hemodynamic parameters has not been previously appreciated. It is also of clinical relevance given recent work highlighting the impact of obesity upon AF prevalence²⁵ and worsened outcomes post AF ablation²⁶, and the increasing likelihood of obese patients presenting for AF ablation²⁷. Given the typical use of absolute weight for most dosing regimes, this was utilized for our analysis; however, a similar relationship was also demonstrated when data was stratified according to ideal body weight or body mass index.

Limitations

Several limitations need to be noted in this study. Firstly, this study focused specifically on adenosine and did not test ATP. Although other studies suggest that the potency of ATP at identical doses is lower than adenosine, given we did not specifically test ATP and its subtly differing pharmacokinetic profile to adenosine, conclusions from this study regarding the dose response relationship of ATP should be made with caution. Secondly, patients failing to manifest AV block at maximal dose (24mg) may have demonstrated AVB at higher doses; however, this would have required adenosine doses beyond current dosing guidelines and as such this was not performed. Thirdly, testing of the veins with adenosine immediately following isolation may

have resulted in under-identification of dormant conduction. Lastly, in those patients with adenosine-mediated reconnection, whether the increased RF time was due to the achievement of initial PVI or due to additional RF applied to extinguish adenosine-mediated reconnection, was indistinguishable. The increased RF time noted should be interpreted in this context.

Conclusions

In patients undergoing adenosine testing for dormant PV conduction following PVI, an adenosine dose sufficient to cause AVB is required to unmask dormant PV conduction. AVB in response to adenosine is significantly reduced in patients weighing more than 110kgs. . Patient weight and variable adenosine dosing may in part explain the conflicting results of studies evaluating the role of adenosine to improve freedom from AF following PVI.

References

- [1] Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J: Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. *N Engl J Med* 1998; 339:659-666.
- [2] Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P, Investigators SAI: Approaches to catheter ablation for persistent atrial fibrillation. *The New England journal of medicine* 2015; 372:1812-1822.
- [3] Chan KH, Sy RW: Toward permanent pulmonary vein isolation: the use of adenosine to unmask dormant conduction. *Heart rhythm : the official journal of the Heart Rhythm Society* 2013; 10:636-637.
- [4] Datino T, Macle L, Chartier D, Comtois P, Khairy P, Guerra PG, Fernandez-Aviles F, Nattel S: Differential effectiveness of pharmacological strategies to reveal dormant pulmonary vein conduction: a clinical-experimental correlation. *Heart rhythm : the official journal of the Heart Rhythm Society* 2011; 8:1426-1433.
- [5] Kobori A, Shizuta S, Inoue K, Kaitani K, Morimoto T, Nakazawa Y, Ozawa T, Kurotobi T, Morishima I, Miura F, Watanabe T, Masuda M, Naito M, Fujimoto H, Nishida T, Furukawa Y, Shirayama T, Tanaka M, Okajima K, Yao T, Egami Y, Satomi K, Noda T, Miyamoto K, Haruna T, Kawaji T, Yoshizawa T, Toyota T, Yahata M, Nakai K, Sugiyama H, Higashi Y, Ito M, Horie M, Kusano KF, Shimizu W, Kamakura S, Kimura T, Investigators U-AT: Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: the UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate (UNDER-ATP) trial. *European heart journal* 2015; 36:3276-3287.
- [6] Macle L, Khairy P, Weerasooriya R, Novak P, Verma A, Willems S, Arentz T, Deisenhofer I, Veenhuyzen G, Scavée C, Jaïs P, Puererfellner H, Levesque S, Andrade JG, Rivard L, Guerra PG, Dubuc M, Thibault B, Talajic M, Roy D, Nattel S: Adenosine-guided pulmonary vein isolation for

the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial. *The Lancet* 2015; 386:672-679.

[7] Efremidis M, Letsas KP, Lioni L, Vlachos K, Georgopoulos S, Saplaouras A, Geladari E, Giannopoulos G, Liu T, Deftereos S, Sideris A: Adenosine-Guided Pulmonary Vein Antral Isolation for Paroxysmal Atrial Fibrillation: A Randomized Study. *J Cardiovasc Electrophysiol* 2016;26:doi:10.1111/jce.13059.

[8] Miyazaki S, Kobori A, Hocini M, Shah AJ, Komatsu Y, Taniguchi H, Kusa S, Uchiyama T, Nakamura H, Hachiya H, Isobe M, Hirao K, Haissaguerre M, Takahashi A, Iesaka Y: Clinical utility of adenosine-infusion test at a repeat atrial fibrillation ablation procedure. *Heart rhythm : the official journal of the Heart Rhythm Society* 2013; 10:629-635.

[9] Anter E, Contreras-Valdes FM, Shvilkin A, Tschabrunn CM, Josephson ME: Acute pulmonary vein reconnection is a predictor of atrial fibrillation recurrence following pulmonary vein isolation. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing* 2014; 39:225-232.

[10] McLellan AJ, Kumar S Fau - Smith C, Smith C Fau - Morton JB, Morton Jb Fau - Kalman JM, Kalman Jm Fau - Kistler PM, Kistler PM: The role of adenosine following pulmonary vein isolation in patients undergoing catheter ablation for atrial fibrillation: a systematic review.

[11] Ghanbari H, Jani R, Hussain-Amin A, Al-Assad W, Huether E, Ansari S, Jongnarangsin K, Crawford T, Latchamsetty R, Bogun F, Morady F, Oral H, Chugh A: Role of adenosine after antral pulmonary vein isolation of paroxysmal atrial fibrillation: A randomized controlled trial. *Heart rhythm : the official journal of the Heart Rhythm Society* 2016; 13:407-415.

[12] Miyazaki S, Taniguchi H, Uchiyama T, Kusa S, Nakamura H, Hachiya H, Hirao K, Iesaka Y: Impact of low-dose dipyridamole injection on adenosine test after pulmonary vein isolation. *Pacing and clinical electrophysiology : PACE* 2013; 36:1451-1459.

[13] Datino T, Macle L, Qi XY, Maguy A, Comtois P, Chartier D, Guerra PG, Arenal A, Fernandez-Aviles F, Nattel S: Mechanisms by which adenosine restores conduction in dormant canine pulmonary veins. *Circulation* 2010; 121:963-972.

[14] Belardinelli L, Shryock Jc Fau - Song Y, Song Y Fau - Wang D, Wang D Fau - Srinivas M, Srinivas M: Ionic basis of the electrophysiological actions of adenosine on cardiomyocytes. *FASEB J* 1995; 9:359-365.

[15] Brunelli M, Raffa S, Grosse A, Hanazawa K, Sammut M, Roos M, Frommhold M, Wauters K, Geller JC: Residual conduction after pulmonary vein isolation with a circular multielectrode radiofrequency ablation catheter: the role of adenosine and orciprenalin during a prolonged observation time. *International journal of cardiology* 2013; 168:4122-4131.

[16] Elayi CS, Di Biase L, Bai R, Burkhardt JD, Mohanty P, Santangeli P, Sanchez J, Hongo R, Gallinhouse GJ, Horton R, Bailey S, Beheiry S, Natale A: Administration of isoproterenol and

adenosine to guide supplemental ablation after pulmonary vein antrum isolation. *J Cardiovasc Electrophysiol* 2013; 24:1199-1206.

[17] Matsuo S, Yamane T, Date T, Lellouche N, Tokutake K, Hioki M, Ito K, Narui R, Tanigawa S, Nakane T, Tokuda M, Yamashita S, Aramaki Y, Inada K, Shibayama K, Miyanaga S, Yoshida H, Miyazaki H, Abe K, Sugimoto K, Taniguchi I, Yoshimura M: Dormant pulmonary vein conduction induced by adenosine in patients with atrial fibrillation who underwent catheter ablation. *American heart journal* 2011; 161:188-196.

[18] Miyazaki S, Kuwahara T, Kobori A, Takahashi Y, Takei A, Sato A, Isobe M, Takahashi A: Impact of adenosine-provoked acute dormant pulmonary vein conduction on recurrence of atrial fibrillation. *J Cardiovasc Electrophysiol* 2012; 23:256-260.

[19] Belhassen B, Pelloe A: Adenosine triphosphate and adenosine: Perspectives in the acute management of paroxysmal supraventricular tachycardia. *Clinical Cardiology* 1985; 8:460-464.

[20] Favale S Fau - Di Biase M, Di Biase M Fau - Rizzo U, Rizzo U Fau - Belardinelli L, Belardinelli L Fau - Rizzon P, Rizzon P: Effect of adenosine and adenosine-5'-triphosphate on atrioventricular conduction in patients.

[21] Arujuna A, Caulfield D, Karim R, Knowles B, Rinaldi A, Cooklin M, Oneill M, Rhode K, Gill J, Razavi R: Acute pulmonary vein isolation lesions consist of interstitial oedema and tissue necrosis: possible mechanism of pulmonary vein reconnection. *Journal of Cardiovascular Magnetic Resonance* 2011; 13:M8.

[22] Jiang CY, Jiang Rh Fau - Matsuo S, Matsuo S Fau - Liu Q, Liu Q Fau - Fan Y-Q, Fan Yq Fau - Zhang Z-W, Zhang Zw Fau - Fu G-S, Fu GS: Early detection of pulmonary vein reconnection after isolation in patients with paroxysmal atrial fibrillation: a comparison of ATP-induction and reassessment at 30 minutes postisolation.

[23] Das M, Wynn GJ, Morgan M, Ronayne C, Waktare JE, Todd DM, Hall MC, Snowdon RL, Modi S, Gupta D: Reablated Sites of Acute Reconnection After Pulmonary Vein Isolation Do Not Predict Sites of Late Reconnection at Repeat Electrophysiology Study. *J Cardiovasc Electrophysiol* 2016; 27:381-389.

[24] Feldschuh J, Enson Y: Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation* 1977; 56:605-612.

[25] Abed HS, Samuel CS, Lau DH, Kelly DJ, Royce SG, Alasady M, Mahajan R, Kuklik P, Zhang Y, Brooks AG, Nelson AJ, Worthley SG, Abhayaratna WP, Kalman JM, Wittert GA, Sanders P: Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. *Heart rhythm : the official journal of the Heart Rhythm Society* 2013; 10:90-100.

[26] Chilukuri K, Dalal D, Gadrey S, Marine JE, Macpherson E, Henrikson CA, Cheng A, Nazarian S, Sinha S, Spragg D, Berger R, Calkins H: A prospective study evaluating the role of obesity and obstructive sleep apnea for outcomes after catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2010; 21:521-525.

[27] Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P: Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. Journal of the American College of Cardiology 2014; 64:2222-2231.

Tables

Table 1 Baseline characteristics of the study population. BMI = body mass index, IHD = Ischaemic heart disease, LAVI = left atrial volume index (to body surface area), LVEF = left ventricular ejection fraction,

Baseline Characteristics (n=50)	
Age (years)	63 ± 9
Gender (% male)	66%
Hypertension	52%
Diabetes	18%
IHD	20%
Heart Failure (LVEF<50%)	12%
Previous stroke	2%
% Persistent	28%
Previous DCR	34%
SR at procedure	72%
Time since diagnosis (years)	5.24 ± 5.9
LVEF	58.9 ± 6.7%
LA area cm ²	24.6 ± 6.9

LAVI ml/m²	41.7 ± 12.7
Antiarrhythmic meds	90%
Anticoagulation	70%
Average BMI	28.3 ± 5.2
Average Weight	86.1 ± 19.0

Table 2 Procedural characteristics of the study population. RF = radiofrequency

Procedural Characteristics	
Pulmonary vein isolation	100%
Posterior wall isolation	18%
Cavotricuspid Isthmus	36%
Other ablation (slow pathway, focal atrial tachycardia ablation)	6%
Fluoroscopy time	13.6 ± 4.0 mins

RF time	43.5 ± 9.0 mins
Procedure time	164 ± 43 mins
Radiation dose	65.6 ± 34.8 mGy

Table 3 The incidence of adenosine medicated and spontaneous reconnection (by vein) in the study population.

Adenosine Reconnection	Spontaneous Reconnection		
	Yes	No	Totals
Yes	7 (33%)*	14 (67%)	21
No	18 (11%)*	152 (89%)	170
Totals	25	166	191

*p=0.004, OR=4.22 (95%CI: 1.51 – 11.83).

Table 4 Measured electrophysiological parameters following administration of each adenosine dose.

N=50 patients	12mg	18mg	24mg	p value	p value	p value
N=339 doses	n=113	n=113	n=113	(12 vs. 18)	(18 vs. 24)	(12 vs. 24)
Baseline PR (ms)	179 ± 56.7	183 ± 59.0	182 ± 59.2	0.62	0.96	0.66

Time to PR lengthening (s)	16.2 ± 4.9	15.7 ± 4.8	14.9 ± 5.4	0.49	0.22	0.06
Time to AV block (s)	17.0 ± 4.9	16.6 ± 4.2	16.7 ± 5.4	0.54	0.89	0.69
Any AV block (% doses)	81.5%	90.5%	92.4%	0.059	0.62	0.019
Duration of AV block (s)	12.0 ± 8.9	16.1 ± 9.1	19.0 ± 9.3	0.001	0.025	<0.001
PR prolong. to recovery time (s)	28.6 ± 11.2	33.1 ± 11.8	35.4 ± 10.7	0.007	0.145	<0.001
Adenosine Induced AF	4.4%	8.0%	10.6%	0.27	0.49	0.08

Table 5 Measured hemodynamic parameters following administration of each adenosine dose.

MBP = mean blood pressure, SBP = systolic blood pressure.

N=50 patients	12mg	18mg	24mg	p value	p value	p value
N=339 doses	n=113	n=113	n=113	(12 vs. 18)	(18 vs. 24)	(12 vs. 24)

Baseline SBP (mmHg)	112 ± 16.7	114 ± 17.8	113 ± 17.5	0.34	0.51	0.78
Baseline MBP (mmHg)	69.3 ± 13.1	69.9 ± 13.1	66.7 ± 11.1	0.73	0.54	0.79
Nadir SBP (mmHg)	79.7 ± 13.2	73.6 ± 13.0	70.6 ± 11.8	<0.001	0.075	<0.001
Nadir MBP (mmHg)	47.7 ± 9.5	43.2 ± 9.2	41.5 ± 9.2	<0.001	0.15	<0.001
Time to nadir (s)	47.2 ± 9.0	47.4 ± 9.6	48.0 ± 9.0	0.87	0.60	0.48
% drop (SBP)	28.8 ± 10.3	35.3 ± 11.2	37.0 ± 10.1	<0.001	0.21	<0.001
% drop (MBP)	30.5 ± 11.4	37.3 ± 12.8	38.9 ± 12.3	<0.001	0.34	<0.001
Time to BP recovery (s)	73.7 ± 17.4	75.9 ± 16.2	82.8 ± 16.9	0.47	0.017	0.0039

Figure 1A

Figure 1B

Figure 1 Comparisons of doses (A) and occurrence of AV block (B) between veins with and without PV reconnection.

Figure 2

Figure 2 Comparison of adenosine dose per kg and duration of AV block at each dose.

Figure 3A

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	<70kg	70-110kg	>110kg
Patients, n=50 (%)	22%	66%	12%
Number of doses	69	231	39

Figure

3B

Figure 3C

Figure 3 A comparison of occurrence of AV block (A), average duration of AV block (B), and average mean percentage drop in in MBP (C) between each weight group (<70kg, 70-110kg and >110kg). MBP = mean blood pressure.

Figure 4A

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Likelihood of AVB (%)	< 70kg, n=69	70 - 110 kg, n=231	> 110 kg, n=39
12mg	91.3%	84.4%	53.8%
18mg	100%	93.5%	61.5%
24mg	100%	93.5%	69.2%

Figure 4B

Av. Duration of AVB (s)	< 70kg, n=69	70 - 110 kg, n=231	> 110 kg, n=39
12mg	19.8	10.8	7.2
18mg	24.5	14.6	9.9
24mg	27.2	14.6	13.8

Figure 4 Practical dosing guidance for adenosine use in AF ablation. The likelihood (A) and duration (B) of AV block at each adenosine dose tested. AVB = atrio-ventricular block

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Title:

Determining the Optimal Dose of Adenosine for Unmasking Dormant Pulmonary Vein Conduction Following Atrial Fibrillation Ablation: Electrophysiological and Hemodynamic Assessment. DORMANT-AF Study

Date:

2017-01-01

Citation:

Prabhu, S., Mackin, V., McLellan, A. J. A., Tuong, P., Mcglade, D., Ling, L. -H., Peck, K. Y., Voskoboinik, A., Pathik, B., Nalliah, C. J., Wong, G. R., Azzopardi, S. M., Lee, G., Mariani, J., Taylor, A. J., Kalman, J. M. & Kistler, P. M. (2017). Determining the Optimal Dose of Adenosine for Unmasking Dormant Pulmonary Vein Conduction Following Atrial Fibrillation Ablation: Electrophysiological and Hemodynamic Assessment. DORMANT-AF Study. JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY, 28 (1), pp.13-22. <https://doi.org/10.1111/jce.13107>.

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