Atrioventricular Nodal Ablation in Atrial Fibrillation
A Meta-Analysis and Systematic Review

Neal A. Chatterjee, MD; Gaurav A. Upadhyay, MD; Kenneth A. Ellenbogen, MD; Finlay A. McAlister, MD, MSc; Niteesh K. Choudhry, MD, PhD; Jagmeet P. Singh, MD, DPhil

Background—In the treatment of patients with refractory atrial fibrillation (AF), the safety and efficacy of atrioventricular nodal ablation (AVNA) versus pharmacotherapy alone remains unclear. Additionally, the impact of AVNA in patients with reduced systolic function is of growing interest.

Methods and Results—A total of 5 randomized or prospective trials were included for efficacy review (314 patients), 11 studies for effectiveness review (810 patients), and 47 studies for safety review (5632 patients). All-cause mortality was similar between AVNA and medical therapy (3.1% versus 3.3%; relative risk ratio, 1.05; 95% confidence interval [CI], 0.29–3.85). There was no significant difference in exercise duration or ejection fraction (EF) with AVNA relative to pharmacotherapy. In subgroup analysis, patients with baseline systolic dysfunction (116 patients; mean EF, 44%) showed significant relative improvement in EF after AVNA (+4% greater; 95% CI, 3.11–4.89). In pooled observational analysis, AVNA was also associated with significant improvement in EF only in patients with systolic dysfunction (+7.44%; 95% CI, 5.4–9.5). The incidence of procedure-related mortality (0.27%) and malignant arrhythmia (0.57%) was low. At mean follow-up of 26.5 months, the incidence of sudden cardiac death after AVNA was 2.1%. There was significant heterogeneity in quality-of-life scales used; compared with pharmacotherapy, AVNA was associated with significant improvement in several symptoms (palpitations, dyspnea).

Conclusions—In the management of refractory AF, AVNA is associated with improvement in symptoms and quality of life, with a low incidence of procedure morbidity. In patients with reduced systolic function, AVNA demonstrates small but significantly improved echocardiographic outcomes relative to medical therapy alone. **(*Circ Arrhythm Electrophysiol*. 2012;5:68-76.)**

Key Words: atrioventricular node ■ ablation ■ pacing ■ fibrillation ■ meta-analysis

Atrial fibrillation (AF) and heart failure (HF) have been characterized as 2 major epidemics of contemporary cardiovascular medicine.[1] AF, the most common clinically significant arrhythmia, affects approximately 2.2 million patients in the United States alone,[2] whereas HF prevalence is estimated at 5.3 million.[3] AF and HF are inextricably linked, as both share common risk factors[4] and each increases the risk of the other.[5] The prevalence of AF increases with HF severity, ranging from <5% in functional class I patients compared with approximately 50% in class IV patients.[6] Inversely, the life-time prevalence of HF in AF has been estimated at 42%.[5]

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Several randomized trials in AF,[7,8] including those exclusive to patients with left ventricular systolic dysfunction (LVSD),[9] have shown similar efficacy with rate versus rhythm control strategies. Although pharmacotherapy remains the first-line approach for effective rate control, ablation of the atrioventricular node (AVNA) with subsequent pacing is an important therapeutic option for patients with symptoms refractory to pharmacotherapy.[10] Compared with pharmacological therapy alone, the so-called "ablate and pace" approach offers the potential for more robust control of ventricular rate as well as regularization of the R-R interval. Given the relationship between AF and HF, there may be particular benefit of such rate and interval control in patients with AF and reduced systolic function. Indeed, several observational and retrospective studies illustrate symptomatic,[11,12] echocardiographic,[13–15] and functional benefit[16,17] after AVNA in patients with AF and LVSD.

Because comparative data are limited, we performed a meta-analysis to evaluate the efficacy of AVNA versus pharmacotherapy in patients with refractory atrial fibrillation,

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From the Department of Medicine and the Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA (N.A.C., G.A.U., J.P.S.); the Division of Cardiology, Virginia Commonwealth University School of Medicine, Richmond, VA (K.A.E.); the Division of Internal Medicine, University of Alberta Hospital, Edmonton, Canada (F.A.M.); and the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (N.K.C.).

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Correspondence to Jagmeet Singh, MD, DPhil, Cardiac Arrhythmia Service, GRB 109, Massachusetts General Hospital Heart Center, 55 Fruit St, Boston, MA 02411. E-mail jsingh@partners.org

including subset analysis comparing patients with reduced versus normal systolic function. Additionally, we assessed the effectiveness of AVNA using pooled outcomes from observational studies and also present a systematic review of safety outcomes from both randomized and observational data.

Methods

Search Strategy

We performed an electronic literature search of MEDLINE (1948 to June 2011), MEDLINE In-Process and Other Non-Indexed Citations, Cumulative Index to Nursing and Allied Health Literature, the Cochrane Database of Systematic Reviews (Fourth Quarter, 2010), the American College of Physicians Journal Club (1991 to January 2011), Database of Abstracts of Reviews of Effects, and the Cochrane Central Register of Controlled Trials. Search terms included atrial fibrillation, heart failure, ablation, and atrioventricular. The search strategy was not exclusive to patients with heart failure (see online-only Data Supplement Appendix). We also handsearched the bibliographies of all review articles discussing atrial fibrillation and AVNA, published in the last 10 years.

For efficacy analysis, we included published data from randomized, controlled trials or prospective cohort studies with contemporaneous controls, comparing AVNA with right ventricular (RV)-only pacing versus pharmacotherapy. For effectiveness analysis, we included published data from observational prospective or retrospective cohort studies; single-arm studies were included for particular end points. For safety analysis, we included randomized, prospective, and retrospective studies. We selected studies reporting mortality (all-cause and/or sudden cardiac death), adverse outcomes, echocardiographic data (eg, ejection fraction [EF]), and/or functional outcomes (eg, exercise stress duration, quality of life [QOL]). Arrhythmia inclusion criteria included atrial fibrillation, atrial flutter, or atrial tachycardia. Pacing inclusion criteria was RV pacing. Reports that included heterogeneous ablation procedures (eg, AV node modification) were excluded, as were studies with $n<20$ who underwent AVNA, non–radiofrequency ablation methods (eg, direct current), studies with heterogeneous arrhythmias (eg, incessant sinus tachycardias, AV nodal reentry tachycardias), studies only examining biventricular (BiV) pacing in AF with AVNA, and studies that did not represent original research data (eg, letters, commentaries, reviews, or study design articles). Studies <2 weeks in duration were excluded from consideration for efficacy and effectiveness analyses but were included in safety analysis.

Data Extraction

Two investigators (Drs Chatterjee and Upadhyay) independently extracted data on patient and study characteristics, outcomes, and study quality for each trial, using a standardized protocol. The PRISMA and MOOSE checklists were used for extraction of randomized, controlled and observational data, respectively. Quality assessment was performed using the Jadad scale[18] for randomized, controlled trials and the Downs and Black checklist[19] for observational studies. Disagreements were resolved by consensus.

Data Analysis

We calculated relative risks for dichotomous outcomes (eg, mortality) by using the Mantel-Haenszel random-effects model in Review Manager 5.1 (The Cochrane Collaboration, Copenhagen, Denmark). For continuous outcomes, weighted mean differences were calculated using an inverse variance random effects model. Heterogeneity was quantified by using the I^2 statistic (a value of 0% indicates minimal heterogeneity).[20] Study N was taken from end of protocol N to generate maximally conservative estimates of effect size. One study[21] used a crossover design with 2 pacing modes (DDD, VVIR). Only the VVIR group was used to ensure comparability across studies. For efficacy analysis, subgroup analysis was performed with studies comprising patients with reduced systolic function. Effectiveness analysis included studies reporting all-cause mortality, echocardiographic, and functional outcomes. Single-armed studies were included for the echocardiographic and functional end points but not for the all-cause mortality end point, given that interpretation of a pooled mortality rate without contemporaneous controls was not thought to be meaningful. For safety analysis, adverse events included sudden cardiac death (SCD), procedure-related mortality, and procedure-morbidity. Mortality and morbidity were attributed to the procedure if they occurred within 30 days of AVNA, with the exception of "lead failure," which was not time-delimited. SCD within the first 30 days was characterized as a procedure-related death. An overall SCD rate (occurring any time after AVNA) was also tabulated; 95% confidence intervals (CIs) are reported for all results.

Results

Search Results

The initial search yielded 2659 results, of which (1) 5 met our inclusion criteria for efficacy analysis of AVNA and pharmacotherapy,[21–25] (2) 11 met inclusion criteria for effectiveness analysis,[12,16,17,26–33] and (3) 47 met inclusion criteria for safety analysis (Figure 1 and online-only Data Supplement Appendix Table 1).[11,12,14,16,17,21–62] The studies comparing AVNA and pharmacotherapy included 314 patients, of whom 161 underwent AVNA and 153 received pharmacotherapy. Weighted mean follow-up was 10 months (range, 6–12 months). Baseline characteristics, including weighted means and variances for each subgroup, are summarized in Table 1. Two of the efficacy studies ($n=116$)[23,24] comprised patients with reduced systolic function (weighted mean EF, $44\pm4\%$). Prevalence of angiotensin-converting enzyme inhibitor use in these 2 studies was 75% and 72% in the ablation and pharmacotherapy groups, respectively. β-Blocker use was not consistently documented. Of the other 3 efficacy studies, 2 reported a mean EF (weighted mean EF, $57\pm4\%$)[22,25] and the authors of the third study [21] stated that the "majority had normal LV function at the outset."

Four of the 5 efficacy studies comparing AVNA with pharmacotherapy were randomized.[21–23,25] Inclusion criteria included paroxysmal or persistent AF in 4 of 5 studies[21–24] and permanent AF in 1 study.[25] All studies mandated cessation of antiarrhythmic therapy after AVNA unless medications were for a non-AF indication. Medications used in the pharmacotherapy arm were documented in 4 of 5 studies.[21–23,25] One study[25] allowed use of nodal agents (β-blockade, calcium channel blockers) as well as digoxin (not explicitly quantified). Of the remaining 3 studies (pharmacotherapy subgroup $n=66$), most patients received antiarrhythmics (class I: 65%, class III: 49%) or digoxin (47%), with a minority receiving nodal agents (β-blockade, calcium channel blockers: 23%). All efficacy studies included a significant minority of patients with structural heart disease (Table 1), with the exception of 1, in which lone AF was among the inclusion criteria. [24] Pacing mode differed among the efficacy studies: 3 of 5 used rate-adaptive VVI pacing,[23–25] 1 used atrial-synchronous sequential pacing (DDD),[22] and 1 used a crossover strategy with both VVIR and DDDR in the ablation subgroup.[21]

Baseline characteristics for the studies included in the effectiveness and safety analyses are described in full in

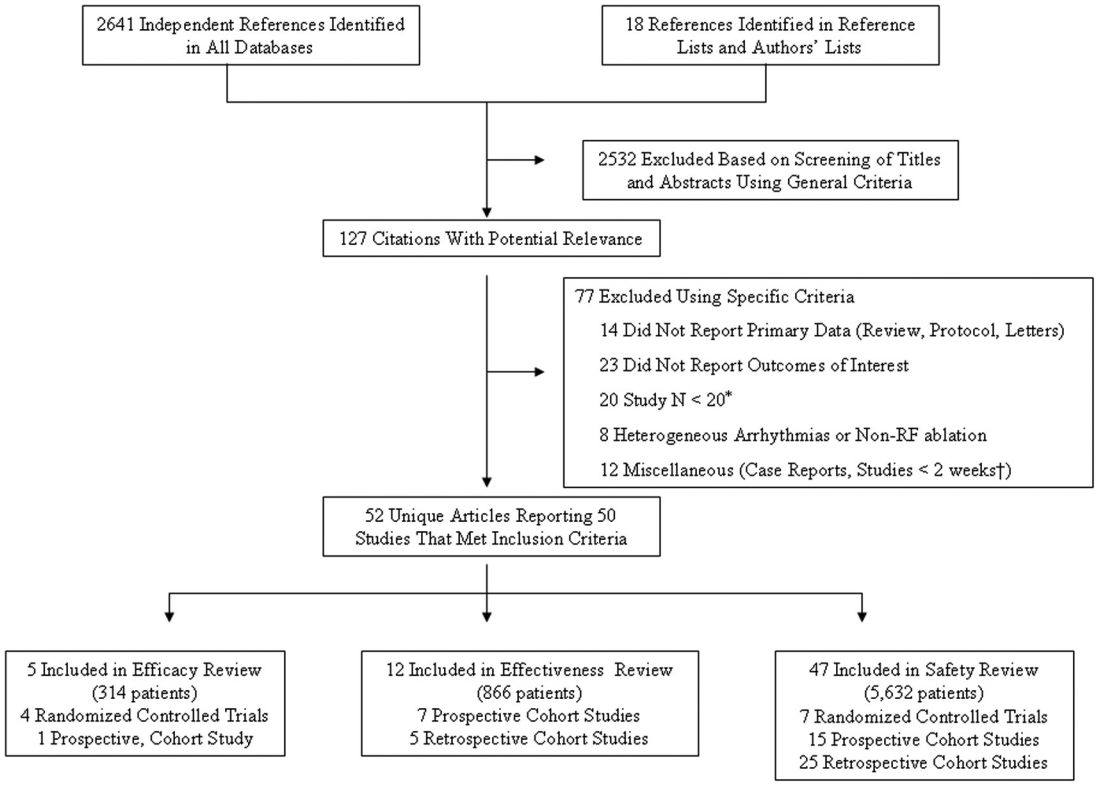

Figure 1. Study flow. *None of the excluded studies with n<20 were randomized. †Study duration <2 weeks was exclusion criteria for effectiveness analysis but not for safety analysis. No studies with study duration <2 weeks were randomized.

online-only Data Supplement Appendix Table 1. Summary demographics include mean age 66±4 years, with slightly more men (58%) and a minority with ischemic heart disease (26%). Of studies reporting EF, the mean was 47±8%.

Efficacy of AVNA

Only 2 studies[23,25] of the 5 studies comparing AVNA and pharmacotherapy had deaths during the study period; there were 10 deaths (5 AVNA; 5 pharmacotherapy) at weighted mean follow-up of 9.8 months, and all deaths occurred at least 1 month after AVNA or study onset (for pharmacotherapy arm). The relative risk of death was not significantly different between AVNA and pharmacotherapy (risk ratio, 1.05; 95% CI, 0.29–3.85), though overall numbers were low. SCD accounted for 60% (3/5) of deaths in the AVNA arm and 100% (5/5) deaths in the pharmacotherapy arm.

All 5 studies comparing AVNA with pharmacotherapy reported changes in tolerance during exercise testing. Three studies used a treadmill test (modified Bruce protocol[24,25] and chronotropic assessment exercise protocol[21]), and 2 used bicycle stress (linear incremental work protocol).[22,23] Both ablation and pharmacotherapy groups showed modest improvement over the study period. There was an insignificant greater relative improvement in patients undergoing ablation, exercising 0.21 minutes longer (95% CI, −0.70 to 1.1), with substantial heterogeneity among studies (I^2=97%). Analysis of studies comprising patients with reduced EF[23,24] versus normal EF[21,22,25] showed no difference between patients with

Table 1. Baseline Characteristics of Studies Included in Efficacy Analysis

	Brignole,[22] 1997		Brignole,[23] 1998		Marshall,[21] 1999		Ueng,[24] 2001		Weerasooryia,[25] 2003	
	AVNA	Meds	AVNA	Meds	AVNA	Meds	AVNA	Meds	AVNA	Meds
No. of patients	22	21	32	34	37	19	21	29	49	50
Age, mean±SD, y	66±10	64±10	72±9	72±9	65±8	60±10	68±6	65±8	68±9	68±9
Male sex, %	45	48	56	38	48.6	63.2	76	66	69	72
CAD, %	27	14	34	41	22	16	NR	NR	43	38
EF, mean±SD, %	58±11	60±10	43±12	44±15	NR	NR	45±6	45±8	55±16	57±14
NYHA class, ±SD	2.9±0.7	2.7±0.7	2.8±0.7	2.7±0.6	NR	NR	2.1±0.7	2.2±0.6	NR	NR
AF duration, y	9±8	8±5	5.7±6.9	4.1±5	7.1±6.3	9.8±8.0	14±7	12±8	4.8±5.5	6.5±10.9

AVNA indicates atrioventricular nodal ablation; Meds, medication; CAD, coronary artery disease; EF, ejection fraction; NYHA, New York Heart Association; AF, atrial fibrillation; NR, not recorded.

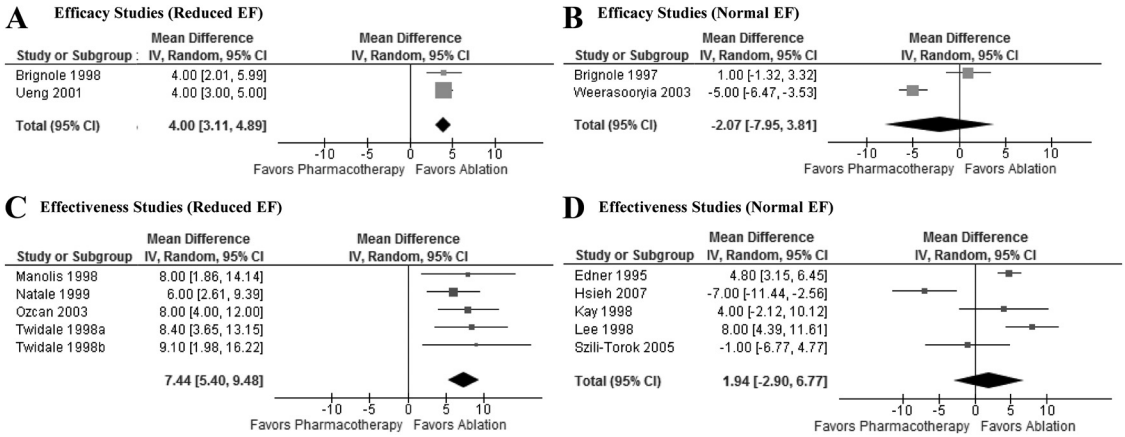

Figure 2. Echocardiographic outcomes stratified by baseline ejection fraction (EF): Efficacy and effectiveness analyses. **A** and **B** show relative change in EF after atrioventricular nodal ablation (AVNA) versus pharmacotherapy for studies comprised of patients with reduced and normal EF, respectively. **C** and **D** show pooled estimates from single-arm observational studies reporting change in EF after AVNA for patients with reduced and normal EF. CI indicates confidence interval.

reduced systolic function (0.40 minutes longer; 95% CI, −1.1 to 1.9) and patients with normal systolic function (−0.02 minutes longer; 95% CI, −0.62 to 0.57). There was no interaction between outcome and type of protocol used (treadmill versus bicycle).

Four studies comparing AVNA with pharmacotherapy reported changes in EF during the study period.[22–25] In all patients, ablation was associated with an insignificant minimal relative increase in EF (+1.0% greater; 95% CI, −3.7 to 5.7), with significant heterogeneity among studies (I^2=97%). In the 2 studies with reduced systolic function (weighted mean EF, 44±4%), there was a modest but significant relative increase in EF after AVNA (+4%; 95% CI, 3.1–4.9) (Figure 2A), with minimal heterogeneity among studies (I^2=0%). In contrast, efficacy studies involving patients with normal EF showed no significant relative change in EF (−2.07%; 95% CI, −8.0 to 3.8) and substantial heterogeneity (I^2=95%) (Figure 2B).

Effectiveness of AVNA

Prospective single-armed studies or any retrospective studies reporting all-cause mortality, echocardiographic, and/or functional outcomes were included in the effectiveness review. Only 1 study (350 patients)[33] included contemporaneous controls and was therefore formally included in the mortality end point of the effectiveness review. Similar to the analysis of randomized, controlled trials, there was no difference in survival between AVNA and matched controls. In a retrospective analysis comparing AVNA versus pharmacotherapy, Ozcan et al[33] found no difference in mortality at a mean follow-up of 36±26 months (risk ratio for AVNA versus pharmacotherapy was 1.14; 95% CI, 0.81–1.60).

Observational studies reporting changes in exercise duration (study n=5; 191 patients) showed a mean increase of 1.19 minutes (95% CI, 0.52–1.86) after AVNA, at mean follow-up of 8.7 months (range, 1–12) (online-only Data Supplement Appendix Figure 1).[17,26,29,30,32]

Observational studies reporting change in EF (study n=10; 389 patients) showed a mean increase of 4.80% (95% CI, 2.01–7.58) after AVNA (weighted mean baseline EF, 43%; range, 26–53%) at a mean follow-up of 13.3 months (range, 1–58).[12,14,16,17,27–32] There was significant heterogeneity across studies (I^2=78%). When stratified by EF, studies with EF <45% (study n=5; 196 patients; weighted mean EF, 35%)[14,16,17,30,32] showed a significant increase in EF after AVNA (+7.44%; 95% CI, 5.4–9.5) with minimal heterogeneity (I^2=0%) (Figure 2C). In contrast, studies with EF >45% (study n=5; 272 patients; weighted mean EF, 47%)[12,27–29,31] showed no significant change in EF (+1.94%; 95% CI, −2.9% to 6.8%) with substantial heterogeneity (I^2=88%) (Figure 2D).

Safety of AVNA

Studies reporting procedural death, procedure morbidity, or SCD were included in safety analysis. Thirty-seven studies reported SCD (n=3756),[11,12,14,16,17,21–27,29–34,36,38,40–43,45–49,51,52,54,55,57,59,60] with an overall incidence of 2.1% (range, 0–11.3%) at a weighted mean follow-up of 26.5 months (range, 1–46). Forty-two studies (n=4886) reported procedural mortality and/or morbidity.[12,14,16,17,21–32,34–37,39–48,50–54,56–62] Most common was the need for left-sided approach after a failed right-sided ablation (6.9%), followed by the need for redo procedures after spontaneous recurrence of AV nodal conduction (2.9%). Other notable procedure-specific morbidities included malignant arrhythmia (sustained VT or VF occurring within 30 days of AVNA; 0.57%), lead failure (0.23%), stroke (0.19%), and hematoma (0.70%) (Table 2). The incidence of procedure-related death, defined as death within 30 days of AVNA, was low (0.27%). Of the total 12 deaths recorded, 5 were reported in a single study in which the postprocedure pacing rate was <70 bpm.[43] Postprocedure pacing rate was inconsistently recorded for several studies, though the majority reported rates >70 bpm, with several studies mandating an initial pacing rate of 80 bpm for at least 7 days.[16,31] Other reported complications included infection, pleural effusion, pericarditis, pseudoaneurysm, RV perforation, and pneumothorax (total incidence, 1.1%). In studies comparing AVNA with pharmacotherapy, there was significant heterogeneity in documentation of pharmacotherapy-related adverse events, with only 1 study documenting

Table 2. Procedural Performance, Morbidity, and Mortality

Adverse Event	Incidence, %
Procedure-related death*	0.27
Procedure performance	
Left-sided ablation†	6.9
Redo procedure‡	2.9
Procedure morbidity*	
Hematoma	0.70
Malignant arrhythmia	0.57
Nonstroke thrombosis	0.27
Lead failure	0.23
Stroke	0.19

*Procedure-related mortality and morbidity were limited to the first 30 days after atrioventricular (AV) nodal ablation (with the exception of "lead failure," which was not time-delimited).

†Refers to failure to achieve AV nodal conduction blockade with an initial right-sided approach.

‡Refers to the incidence of spontaneous recurrence of AV nodal conduction after an initially successful ablation.

medication side effect,[25] 2 documenting incidence of myocardial infarction/stroke,[23,25] and 3 recording episodes of HF/hospitalization.[22–24]

Quality of Life

All 5 studies in the efficacy analysis found significant relative improvement for particular symptoms with AVNA compared with pharmacotherapy alone. Specific QOL and symptom scales used across efficacy studies are summarized in online-only Data Supplement Appendix Figure 2. With respect to QOL, 4 of 5 efficacy studies[22–25] found significant absolute improvement with AVNA compared with baseline, although only 3 of 5 documented significant relative improvement when compared with pharmacotherapy alone[23–25] (see online-only Data Supplement Appendix Figure 2 with probability values for comparison). Although there was significant heterogeneity in the symptom scale used, there was overlap in particular symptoms surveyed. One efficacy study[25] did not explicitly document specific symptoms. Of the remaining 4 efficacy studies, there was absolute significant improvement after AVNA in palpitations (4/4 studies), effort dyspnea (3/4 studies), and easy fatigue (2/3 studies), with less consistently documented absolute improvement in chest discomfort and rest dyspnea (2/4 studies each). When compared relatively with pharmacotherapy, AVNA was associated with significant improvement in palpitations (4/4 studies), effort dyspnea (3/4 studies), and easy fatigue (3/3 studies) but nonsignificant relative improvement in rest dyspnea (0/4 studies) and chest discomfort (1/4 studies).

Of 11 observational studies documenting QOL,[11,12,16,17,29–32,37,54,57] all showed statistically significant improvement of QOL and symptoms after AVNA, though none included a contemporaneous control group. There was significant heterogeneity in QOL scales used in observational studies, which limited summative analysis.

Discussion

Our findings suggest that in patients with refractory AF, AVNA is associated with modest but nonsignificant improvement in functional and echocardiographic outcomes and a significant improvement in symptoms and QOL when compared with pharmacotherapy alone. In a subset analysis of patients with reduced systolic function, improvement in LVEF after AVNA, relative to pharmacotherapy alone, did reach significance. There have been too few deaths reported (n=10) to draw conclusions regarding the effect of AVNA versus pharmacotherapy on mortality. In safety analysis, we found a relatively common incidence of the need for redo procedures or an alternative ablation approach, although the risk of serious adverse events, including malignant arrhythmia and procedure-related death, was small.

To date, there are 2 reported meta-analyses of ablate and pace therapy in AF.[63,64] The report from Wood et al[64] acknowledges the inclusion of a heterogeneous mixture of nonrandomized, randomized, and single-arm studies comprising patients with both normal and reduced systolic function. The second report[63] includes 2 studies[26,65] without a true pharmacotherapy-only control group. Our systemic review contributes to the evidence base by selecting a more homogenous and larger set of studies for both efficacy and safety analyses, as well as providing stratified analysis according to baseline systolic function.

The only retrospective comparison of survival in AF with LVSD found no significant difference in survival between AVNA and pharmacotherapy over a mean follow-up of 3.5 years.[33] Nevertheless, retrospective analysis from the same authors found worse survival with AVNA for patients with LVEF <40% compared with those with EF >40%,[14] and others have found the presence of systolic dysfunction and fractional shortening <20% to be independent predictors of mortality after AVNA.[61] There is a clear need for randomized data assessing the impact of AVNA (RV or BiV pacing) versus pharmacotherapy on survival in the AF population with LVSD.

In addition to overall survival, others have raised concern regarding the incidence of SCD after AVNA.[40,42] Proposed mechanisms include exaggerated repolarization abnormalities after heart rate control in patients with prior tachycardia[66] and absence of an escape rhythm in the event of pacemaker failure.[49,67] The reported incidence of SCD after AVNA has ranged between 1–11% in retrospective studies,[32,40,42,51,64] with LVEF <45%,[42] coronary artery disease, and structural heart disease[51] identified as independent risk factors. Of note, studies finding independent associations between systolic dysfunction and SCD[14,42] were published before the standard use of implantable cardioverter-defibrillator as primary prophylaxis in this population.[68] Similar to the incidence of SCD reported in the last systematic review of AVNA in AF (2.0%),[64] our safety analysis found an overall SCD incidence of 2.1% at mean follow-up of 29.8 months. Exploratory analysis did not find any basic correlation between publication year and SCD rate. As a general comparison, the reported incidence of SCD in patients with AF receiving pharmacotherapy has ranged 3.1–3.8% in trials with similar duration of follow-up, including RACE (mean follow-up, 27.6 months)[69] and AFFIRM (mean follow-up, 42 months).[70]

A primary concern regarding AVNA has been the risk of procedure-related adverse events. We found a very low

incidence of procedure-related death (0.27%) and malignant arrhythmia (0.57%). Indeed, given prior data suggesting that postablation pacing rate reduces the incidence of malignant arrhythmia and death,[43] it is notable that nearly half of the documented procedure-related deaths (5/12) occurred with a postprocedure pacing rate of <70 bpm. The need for a left-sided approach after a failed right-sided ablation was relatively common (6.9%), as was the incidence of redo procedures (2.9%). Other significant procedure morbidities, including stroke, other thrombosis, and lead failure, were rare (<1%). As a reference, recent analysis of recipients undergoing defibrillator implantation noted an adverse event rate of 6.8% over 30 days after the procedure, including pocket hematoma (1.2%), hemothorax/pneumothorax (0.9%), and lead failure (2.2%).[71] Documentation of medication-related adverse events was nonuniform and often not recorded in the randomized studies selected. As a reference, adverse events requiring cessation of therapy in the rate and rhythm control arms of the AFFIRM trial was >30% over mean follow-up of 3.5 years, with significant cardiac, pulmonary, and gastrointestinal toxicities ranging between 2.4–5%.[8]

We found that compared with pharmacotherapy alone, AVNA was associated with a modest but statistically significant improvement in EF for patients with reduced systolic function[23,24] (+4% greater; 95% CI, 3.11–4.89). Pooled observational data analyzed in the present study showed a similar association between AVNA and echocardiographic benefit in patients with systolic dysfunction but not for patients with normal systolic function. Although our prospective findings are similar to prior observational data,[11–17] interpretation of this improvement has several caveats. First, the comparative data in patients with systolic dysfunction reflect the summation of 2 prospective studies, 1 of which was nonrandomized. A disproportionate percentage of the benefit in the efficacy subgroup analysis for reduced EF was derived from the nonrandomized study. Second, the cardiac substrate of patients in these 2 studies was different; 1 study[24] included patients with no known ischemic heart disease, whereas a significant minority of patients in the second study (38%) had ischemic heart disease.[23] Third, given the influence of RV lead position on LV function in AF patients undergoing AVNA,[72] the lack of data regarding RV lead location in these studies may represent an unaccounted confounding variable. Fourth, echocardiographic comparisons across studies would optimally be in the setting of a uniform, paced rate; pacemaker settings during echocardiographic follow-up were not documented in the majority of studies selected.

The optimal treatment of patients with refractory AF, and in particular those with concurrent systolic dysfunction, remains an important open question. The largest prospective study of AF with LVSD found similar benefit between pharmacological rate versus rhythm control,[9] although a small, prospective study[73] found superiority with catheter-based rhythm control (pulmonary vein isolation) compared with device-based rate control (AVNA) in AF with LVSD.

Taken together, available data suggest either AVNA or pharmacotherapy alone is reasonable in the treatment of refractory AF, and that there may be a modest benefit for AVNA in a subset of AF patients with systolic heart failure. These results should be interpreted cautiously, however, because particular subsets of patients with AF who may be detrimentally affected by AVNA and chronic RV pacing, including those with severe mitral or tricuspid regurgitation, pulmonary hypertension, or underlying RV dysfunction, were not identified separately for comparison.[17] This analysis does not address the relative benefit of different nonpharmacologic therapies for AF, including pulmonary vein isolation versus AVNA. Also not addressed by these studies is the relative impact of RV versus BiV pacing in the AF population undergoing AVNA.[36,74] Ongoing studies, including CASTLE-AF[75] (pulmonary vein isolation versus pharmacotherapy), will further define the role of nonpharmacologic therapy for the growing population of patients with AF and systolic dysfunction.

Limitations

These analyses have several limitations, many of which have been discussed. With respect to the efficacy analysis, several outcomes (eg, pacing parameters during echocardiographic follow-up, exercise stress protocols) were nonstandardized across studies, limiting the validity of combining them in a meta-analysis. This lack of standardization is reflected in the heterogeneity for particular outcomes (eg, mean change in exercise stress duration). In addition, given the limited number of total studies and their small sample sizes, the power of summative calculations is limited for outcomes such as mortality. Third, lack of consistent documentation of HF therapeutics, particularly in older observational studies, represents a potential confounder in the interpretation of echocardiographic benefit associated with AVNA. Finally, 1 of the studies included in the efficacy analysis was nonrandomized.

With respect to safety analyses, because studies that did not document survival were excluded from analysis and studies recording no deaths were included, there may be a bias toward underestimating the incidence of SCD. In addition, several studies did not document complications in a systematic manner, and we may therefore be underestimating the overall incidence of procedure-related morbidity. Finally, this analysis excluded patients meeting criteria for and undergoing BiV lead implantation. As such, these safety data may not fully apply to the subset of patients undergoing AVNA, who additionally meet criteria for cardiac resynchronization therapy.

Clinical Implications

AVNA is a safe intervention that improves symptoms and QOL in patients with drug-refractory AF. Compared with pharmacotherapy alone, AVNA may be of particular benefit to patients with baseline reduced systolic function in regard to echocardiographic improvement, although the clinical impact of this difference remains uncertain.

Disclosures

Dr Ellenbogen is a consultant for Biotronik, Boston Scientific, Medtronic, Sorin Group, and St Jude Medical and receives research grants from Medtronic, Boston Science, and St Jude and fellowship support form Medtronic, Boston Science, and Biotro-

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CLINICAL PERSPECTIVE

The optimal treatment of patients with atrial fibrillation refractory to pharmacotherapy, particularly in patients with reduced systolic function, remains unclear. Atrioventricular nodal ablation (AVNA) represents a potential nonpharmacologic therapeutic option in this population. The aim of this study was to assess the efficacy, effectiveness, and safety of AVNA in patients with atrial fibrillation, including patients with systolic dysfunction. A total of 5 randomized or prospective trials were included in efficacy analysis (314 patients), 11 studies for effectiveness review (810 patients), and 47 studies for safety review (5632 patients). Our findings demonstrate that there was no difference in all-cause mortality, exercise duration, and ejection fraction between AVNA and medical therapy. In subgroup analysis, patients with baseline systolic dysfunction showed significant relative improvement in ejection fraction after AVNA compared with patients receiving pharmacotherapy (+4% greater; 95% confidence interval, 3.11–4.89). In pooled observational analysis, AVNA was also associated with significant improvement in ejection fraction only in patients with systolic dysfunction (+7.44%; 95% confidence interval, 5.4–9.5). The incidence of procedure-related mortality (0.27%) and malignant arrhythmia (0.57%) was low. At mean follow-up of 26.5 months, the incidence of sudden cardiac death after AVNA was 2.1%. In the management of refractory atrial fibrillation, AVNA is associated with improvement in symptoms and quality of life, with a low incidence of procedure morbidity. In patients with reduced systolic function, AVNA demonstrates small but significantly improved echocardiographic outcomes relative to medical therapy alone.