Available online at www.sciencedirect.com

ScienceDirect

Journal of Electrocardiology 48 (2015) 861 – 866

JOURNAL OF Electrocardiology

www.jecgonline.com

Non-invasive assessment of the effect of beta blockers and calcium channel blockers on the AV node during permanent atrial fibrillation

Frida Sandberg, PhD,[a,*] Valentina D.A. Corino, PhD,[b] Luca T. Mainardi, PhD,[b] Sara R. Ulimoen, MD, PhD,[c] Steve Enger,[c] Arnljot Tveit, MD, PhD,[c] Pyotr G. Platonov, MD, PhD,[d] Leif Sörnmo, PhD[a]

[a] *Department of Biomedical Engineering and Center for Integrative Electrocardiology at Lund University (CIEL), Lund University, Lund, Sweden*
[b] *Department of Electronics, Information and Bioengineering, Politecnico di Milano, Italy*
[c] *Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, Drammen, 3004, Norway*
[d] *Center for Integrative Electrocardiology at Lund University (CIEL) and Arrhythmia Clinic, Skåne University Hospital, Lund, Sweden*

Abstract

Aim: We aimed at assessing changes in AV nodal properties during administration of the beta blockers metoprolol and carvedilol, and the calcium channel blockers diltiazem and verapamil from electrocardiographic data.

Methods: Parameters accounting for the functional refractory periods of the slow and fast pathways (aRPs and aRPf) were estimated using atrial fibrillatory rate (AFR) and ventricular response assessed from 15-min ECG segments recorded at baseline and on drug treatment from sixty patients with permanent AF.

Results: The results showed that AFR and HR were significantly reduced for all drugs, and that aRPs and aRPf were significantly prolonged in both pathways. The prolongation in aRP was significantly larger for the calcium channel blockers than for the beta blockers.

Conclusions: The changes observed in the AV node parameters are in line with the results of previous electrophysiological studies performed in patients during sinus rhythm, therefore supporting the clinical value of the method.

Keywords: Atrial fibrillation; Atrioventricular node; Rate control; Functional refractory period; Beta blocker; Calcium channel blocker

Introduction

Several randomized clinical trials have shown that rate control may be as effective as rhythm-control medication [1–4] in atrial fibrillation (AF). Therefore, rate control of AF is a commonly used treatment option [5]. According to the current guidelines [5], drugs recommended for rate control include beta blockers, non-dihydropyridine calcium channel antagonists, and digitalis, or their combination. The main determinants of heart rate (HR) during AF are conduction characteristics, refractoriness of the atrioventricular (AV) node and autonomic tone. Rate-control drugs affect AV nodal properties, notably conduction velocity and refractory period, but may also affect atrial properties. Despite the huge number of patients treated with pharmacologic rate control, information is still lacking on how such drugs affect the AV node properties during AF.

During drug development, the effects are usually assessed invasively during sinus rhythm by applying an atrial pacing protocol to determine the refractory period and conduction velocity through the AV node. However, such a protocol cannot be applied in patients with AF. In addition, it is highly desirable to assess the effect of a drug on AV nodal electrophysiology during AF without the need for cardiac catheterization. A noninvasive approach would be useful, e.g., when optimizing therapy as it would help to widen the target patient population during the early clinical phases of drug development.

We have recently developed a method for noninvasive assessment of AV nodal characteristics [6,7] in patients with AF. The method estimates the refractory periods of the two AV nodal pathways, the probability of an impulse passing through the slow pathway, and the prolongation of the refractory periods due to, e.g., concealed conduction. All parameters are estimated from information in the ECG, i.e., f-waves and RR intervals. The method has previously been used for assessing the effect of tecadenoson and esmolol on AV nodal properties in 14 patients with AF [8]. The results

* Corresponding author at: Department of Biomedical Engineering, Lund University, Box 118, SE-22100, Sweden. Tel.: +46 46 2229775.
E-mail address: frida.sandberg@bme.lth.se

http://dx.doi.org/10.1016/j.jelectrocard.2015.07.019
0022-0736/

showed that the parameters reflected expected changes in AV nodal properties, i.e., slower conduction through the AV node for tecadenoson and prolongation of AV node refractory period for esmolol. Moreover, the effect of metoprolol was assessed, with results suggesting that the estimated refractory period can serve as a non-invasive estimate of functional refractory period [9].

Recently, the RATe control in Atrial Fibrillation (RATAF) study compared the effects of four once-daily drug regimens (metoprolol, diltiazem, verapamil, and carvedilol) on HR and arrhythmia-related symptoms in patients with permanent AF [10]. The results showed that HR was significantly lower during treatment with diltiazem than for the other drugs, and that arrhythmia-related symptoms were reduced during treatment with calcium channel blockers, but not with beta blockers.

The aim of the present study is to assess changes in AV nodal properties during administration of metoprolol, carvedilol, diltiazem and verapamil in the RATAF population. The hypothesis is that the effect of these drugs on AV nodal characteristics can be captured by our method, reflecting a prolongation of the refractory periods of the two AV nodal pathways.

Materials and methods

Patients

The present study is based on patient data collected in the RATAF study—a prospective, randomized, investigator-blind crossover study designed to compare four drug regimens (metoprolol 100 mg/day, diltiazem 360 mg/day, verapamil 240 mg/day, and carvedilol 25 mg/day) used for rate control in patients with permanent AF. Each drug was given for at least 3 weeks to ensure an adequate period of washout of the previous treatment and steady-state plasma concentration. Patients who used rate-reducing drugs before inclusion had a 2-week washout period before starting the first study drug. Those taking digitalis had this drug discontinued and did not start the washout period until the digitalis was undetectable in the serum. Before starting the first treatment and on the last day of each of the four treatment periods, 24-h Holter recordings were made. A detailed protocol of the study is described elsewhere [10]. The regional ethics committee and the Norwegian Medicines Agency approved the study, registered at www.clinicaltrials.gov (clinical trial no. NCT00313157) and conducted in accordance with the Helsinki Declaration. Eligible patients were >18 years old, with permanent AF of ≥3 months' duration and a heart rate at rest of ≥80 beats/min or an average heart rate of ≥100 beats/min during the day. The main exclusion criteria were congestive heart failure or ischemic heart disease with the need for concomitant treatment with β blockers, hypotension, treatment with class I or III antiarrhythmic drugs, severe renal or hepatic failure, and pregnancy. Each patient provided written informed consent before any study-related procedures were performed. Sixty patients were included in the study, and their clinical characteristics are presented in Table 1.

Table 1
Demographic characteristics and cardiovascular history in the study population.

Variable	Value
Age (years)	71 ± 9
Gender (male/female)	42/18
AF duration (months)	11 (2–121)
Body mass index (kg/m^2)	27 ± 4
Stroke or transitory ischemic attack	7 (12%)
Diabetes mellitus	3 (5%)
Hypertension	25 (42%)
Chronic obstructive pulmonary disease	3 (5%)
Systolic blood pressure (mm Hg)	141 ± 18
Diastolic blood pressure (mm Hg)	91 ± 10
Left atrial diameter (long-axis view, mm)	50.4 ± 6.6
Left ventricular ejection fraction (%)	61.4 ± 7.5
Warfarin	56 (93%)
Aspirin	4 (7%)
Angiotensin receptor blocker or angiotensin-converting enzyme inhibitor	22 (37%)
Diuretics	9 (15%)
Statins	12 (20%)

Values are expressed as mean ± SD, median (range) or *n* (%).

Atrioventricular node parameters

Using our recently proposed method [6,7], five parameters are estimated from the ECG which characterize electrophysiological properties of the AV node. The method assumes that atrial impulses arrive randomly to the AV node, with a mean arrival rate proportional to atrial fibrillatory rate (AFR). The AFR is determined from the average repetition rate of the f-waves in the ECG [22,23]. Each atrial impulse arriving at the AV node is assumed to result in a ventricular activation, unless blocked by a refractory AV node. The slow and the fast pathways are characterized by their respective absolute refractory period (*aRPs* and *aRPf*; *aRPs* < *aRPf*) and relative refractory period (*rRPs* and *rRPf*), see Fig. 1. Fig. 2 illustrates the processing of the ECG signal for producing the RR series and the AFR, constituting the entire basis for AV node parameter estimation.

Since *aRP* defines the shortest possible interval between conducted impulses, it may serve as a non-invasive estimate of the functional refractory period. The parameter *rRP* accounts for relative refractoriness as well as concealed conduction. The proportion of atrial impulses conducted through the slow AV nodal pathway is quantified by the parameter α. Apart from AFR, the parameters, i.e. *aRPs*, *aRPf*, *rRPs*, *rRPf*, and α, are all estimated from the RR interval series. The estimated parameters are summarized in Table 2. A detailed description of the method and the technique for estimating the parameters can be found in [6,7].

Data analysis

Segments extracted from the 24-h Holter recordings during the same time period were analyzed to account for differences in autonomic nervous system influences during the day. Since the peak of the rate-reducing effect of the drugs was found to be in the afternoon [10], the 15-min segment closest to 14:00 was selected, provided that the signal quality allowed AFR estimation. Recordings were