cardioversion procedure, then the outcome of the latter strategy is not successful. In addition, long-term arrhythmia outcome, even when administering amiodarone, is poor. Therefore, in these patients, amiodarone and repeated electrical cardioversion should be avoided as much as possible. To our surprise, immediate reinitiation of AF was also associated with a high incidence of conversion to sinus rhythm with amiodarone without the need for subsequent electrical cardioversion. In patients with persistent AF the average conversion rate during 1 month of amiodarone loading amounts to only 15% to 20%.

Taken together, our data indicate that immediate reinitiation of AF is an important sign that may help to guide further treatment in patients resisting elective electrical cardioversion for persistent AF. Patients with failed electrical cardioversion due to immediate reinitiation of AF deserve a second chance taking amiodarone combined with electrical cardioversion if still needed. This approach is effective, especially since almost half of these patients achieve successful conversion with amiodarone alone.

In patients with AF resisting electrical cardioversion due to immediate reinitiation of the arrhythmia after the shock, 91% of patients maintain long-term sinus rhythm taking amiodarone and undergoing repeat cardioversion. Thus, immediate reinitiation of AF is an important sign that should guide further treatment in patients with electrical cardioversion–resistant AF.


Acute Electrophysiologic Effect of Estradiol 17β in Menopausal Women

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Clinical studies have led to the suggestion that estrogen deficiency or estrogen-progestin imbalance may be associated with an increased incidence of cardiac arrhythmias such as those occurring during the luteal phase of the menstrual cycle, during oral contraceptive treatment, and during pregnancy and menopause.1–3 In particular, menopause is associated with an increased incidence of palpitations, most of which are due to supraventricular arrhythmia. These palpitations may be partially related to the alteration of the autonomic nervous control of the cardiovascular system, and partially to the changes in the ovarian hormone profile, which occur with menopause. If the electrophysiologic properties of estrogen shown in vitro are proved to occur also in vivo, then the lack of these hormones may be responsible, in part, for the palpitations reported during menopause. This study investigates whether the acute administration of estradiol 17β has an effect on the electrophysiology of the human heart in menopausal women.

The study population included 18 menopausal women (mean age 59 ± 6 years) referred for an electrophysiologic study as a part of a follow-up evaluation of the results of radiofrequency catheter ablation. None had detectable structural heart disease and all had documented repetitive supraventricular tachyarrhythmias. Menopause was defined by the absence of menstrual cycles for at least 6 months, by 17β plasma estradiol levels of <100 pmol/L and by follicle-stimulating hormone levels >40 IU. In 4 patients menopause was due to bilateral oophorectomy. Patients with heart failure (New York Heart Association class >II), coronary, valvular, or myocardial disease, and hypertension (blood pressure >160/90 mm Hg) were excluded from the study. Patients taking hormone replacement therapy in the 6 months preceding the study were also excluded. Clinical characteristics of the study patients are listed in Table 1.

All patients were studied while fasting and after all antiarrhythmic drugs had been withdrawn for at least 3 weeks. Three tetrapolar standard 6Fr catheters with interelectrode spacings of 2 or 5 mm were inserted through the left or right femoral and left subclavian veins, and positioned in the upper right atrium near the sinus node region and at the atrioventricular junction.

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to record the His bundle electrogram, and in the right ventricular apex. One 7Fr decapolar electrode with an internal lumen and interelectrode spacings of 2 to 5 mm (Bristol Myers Squibb, Princeton, New Jersey) was positioned into the coronary sinus. Leads I, II, V1, and the intracardiac electrocardiogram were simultaneously recorded by a Bard EP Lab System recorder (C.R. Bard Inc., Lowell, Massachusetts), in a bipolar fashion at a paper speed of 100 or 200 mm/s and filtered between 30 and 500 Hz. Electrical stimulation was delivered by a programmable stimulator (Medtronic, model 5238, Minneapolis, Minnesota) with a pulse duration of 2 ms and an amplitude twice the diastolic threshold. Catheter position was checked under monoplane fluoroscopy. Before the stimulation protocol, the basal interval were measured: PA interval, the interval from beginning of P on electrocardiogram to first atriogram component recorded at His level; AH interval, conduction time from the low right atrium to the His bundle; and HV interval, conduction time from proximal His bundle to the ventricular myocardium. The stimulation protocol for the electrophysiologic study included (1) incremental synchronized atrial pacing performed from the high right atrium in the region of the sinus node. It was begun at a cycle length just below that of sinus rhythm, with progressive shortening of the cycle length in 10- to 10-ms decrements, to a minimum of 250 ms and/or a cycle length at which atrioventricular Wenkebach phenomenon occurred. Each paced cycle length was maintained for 20 to 30 seconds to ensure stability of conduction intervals and to avoid the influence of autonomic tone and hemodynamic effects; the study also included a programmed stimulation with single and double extrastimuli from the high right atrium and right ventricle apex. The extrastimulus was delivered after a train of 8 paced complexes to allow time for stabilization of refractoriness. The protocol was repeated at 2 different drive cycles (700 and 600 ms), and the extrastimulus was introduced at progressively shorter coupling intervals until a response was no longer elicited (effective refractory period). The interval between each programmed stimulation was 3 seconds and the measurements were obtained at the site of stimulation (atrium and ventricle, respectively). Right intra-atrial and atrioventricular conduction times (PA, AH, HV), functional atrioventricular nodal conduction time, and right atrial and right ventricular effective refractory periods were measured.

After a baseline electrophysiologic study, patients were randomized to receive either sublingual estradiol 17β (1 mg, Estrace Bristol-Myers Squibb, Princeton, New Jersey) or sublingual placebo in a double-blind fashion. Thirty minutes after administration of the study drug, the electrophysiologic study was repeated with the same protocol and stimulation of the same sites. Blood samples were obtained from the coronary sinus to measure 17β estradiol levels before administration of the study drug and at the end of the study.

The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all patients.

Intracardiac electrocardiographic tracings were analyzed independently and in a blinded manner by 2 experienced investigators using a computer-assisted system. Intervals and duration of the electrocardiographic waves were measured in milliseconds. Unpaired 2-tailed nonparametric tests were performed to assess statistical significance of differences observed between groups. A 2-way analysis of variance was performed to assess statistical differences before and after interventions within groups. A p value <0.05 was considered significant.

Two patients were excluded from the study because of the presence of an asymptomatic atrioventricular concealed accessory pathway detected during baseline electrophysiologic study. Therefore, the study group included 16 menopausal women whose baseline electrophysiologic study showed normal intra-atrial and atrioventricular conduction. After the baseline study, 8 patients were randomized to receive 1 mg of sublingual estradiol 17β (group A) and 8 to receive sublingual placebo (group B). The 2 groups had similar clinical characteristics and baseline electrophysiologic parameters (Tables 1 and 2). No changes in electrophysiologic parameters were detected in group B patients after administration of placebo. In group A, estradiol 17β significantly increased the PA interval by 16%, the AH interval by 20%, and the right atrial effective refractory period by 5% (Table 2). In these patients, estradiol 17β plasma levels significantly increased (8.57 ± 6.62 vs 157.5 ± 86.68 pg/L, p <0.05), whereas no differences in estradiol 17β were observed in group B before and after administration of placebo (8.16 ± 4.5 vs 12 ± 10.6 pg/L, p = NS). The percent changes in electrophysiologic parameters after administration of either estradiol 17β or placebo are shown in Figure 1.

The present study shows that acute administration of estradiol 17β affects electrical conduction within the right atrium and prolongs the absolute refractory period in this cardiac chamber. A trend toward a prolongation of atrioventricular conduction was also observed. These observations confirm that estradiol 17β has electrophysiologic properties also in vivo. These properties may play a relevant role in the transmission of the electrical signal within cardiac chambers. Accordingly, estrogen deprivation states or estrogen/progestin imbalance may be of importance in facilitating arrhythmias in a variety of cardiac conditions.1-3 Menopause is often associated with an increased incidence of palpitations and with worsening

| TABLE 1 Baseline Clinical Characteristics of Patients Randomized to Estradiol 17β or Placebo |
|-----------------------------------------------|---------------------|
| Variable                        | Group A (n = 8) | Group B (n = 8) |
| Mean age (yrs)             | 58 ± 8         | 60 ± 5          |
| Menopausal age (yrs)       | 46 ± 5         | 46 ± 8          |
| Estradiol plasma levels (pg/L) | 9 ± 7          | 8 ± 4          |

p <0.05
of preexisting arrhythmias. This may be partly related to the increase in sympathetic activity that occurs with the cessation of menses, but may also be directly related to the lack of ovarian hormones. Our group has recently shown that in young women, episodes of paroxysmal supraventricular tachycardia have a cyclical variation that inversely correlates with the plasma levels of estradiol 17β. This suggests that the levels of this hormone may be important in modulating the occurrence of cardiac arrhythmias in women.

The electrophysiologic effects of estrogens that we report in this study are likely to be related to the electrophysiologic effects of estradiol 17β as suggested by in vitro studies. Harder and Coulson and Jiang et al showed that in vitro estradiol 17β affects potassium and calcium flux through membrane channels in smooth muscle cells and in cardiac myocytes. Mechanisms such as catecholamine release and uptake in vivo, which are also influenced by circulating estrogen levels, may play a role in influencing electrophysiologic properties of cardiac myocytes in women. The plasma levels of estradiol 17β achieved in this study were similar to those observed during chronic estrogen replacement therapy, thereby suggesting that the dose of estrogen used during long-term hormone replacement therapy may exert effects relevant for chronic use. Estrogen deficiency is unlikely to cause cardiac arrhythmias, per se, although it may worsen preexisting rhythm disorders. Little is known about the electrophysiologic effect of progesterone, but because this hormone opposes estrogens, it may exert a facilitatory effect on cardiac arrhythmias. A direct correlation between episodes of arrhythmias and plasma progesterone levels has been shown in women with regular menstrual cycles. Therefore, estrogen-progestin imbalance may be of importance in some forms of arrhythmia, such as those occurring during menses or during the use of oral contraceptives.

In conclusion, the present study suggests that acute administration of estradiol 17β, at a dose achieving plasma levels of the hormone similar to those observed with chronic estrogen replacement therapy, has a significant electrophysiologic effect in menopausal women.