AMIODARONE FOR CONVERSION OF PAROXYSMAL ATRIAL FIBRILLATION IN CONGESTIVE HEART FAILURE

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Summary. Congestive heart failure (CHF) is one of the leading causes of atrial fibrillation (AF), because it increases risk of AF 5 times. Approximately one fifth of CHF patients has AF, which impedes hemodynamic status, increases risk for both stroke and mortality. Conversion of AF to sinus rhythm partially alleviates bad prognosis. The opposite is also true, because in CHF patients AF increases risk of stroke; it may be considered that AF and CHF make one another substantially worse. Critical analysis of published studies and articles suggests amiodarone for the drug of choice for conversion of AF in patients with CHF, due to safety and efficacy, incl. minimal negative inotropic and proarrhythmic effect. We analyzed 20 hospitalized patients with paroxysmal (< 48h) AF and CHF (mostly due to coronary artery disease and hypertension). Amiodarone was applied in loading doses (800 - 1200 mg daily). Oral anticoagulant therapy with warfarin was “overlapped” with low - molecular- weight heparin (LMWH) Fraxarin, and for this purpose LMWH is superior to standard heparin, according to our experience. At discharge, 18 patients (90%) were in sinus rhythm, with average time to conversion 6.1 ± 3.8 days. One month later the percentage increased to 95%, because one another patient was converted. In all patients the reduction of heart rate was evident. Following unwanted effects were found: often increased QTc interval (without ventricular tachycardias of torsade type), first degree AV block in 4 patients, and especially difficulties in maintaining optimal range of warfarin efficacy, with INR increases up to 5, but without manifest bleedings. Literature data and our own experience for many years led us to conclusion that amiodarone is the drug of choice for medicament conversion of paroxysmal atrial fibrillation in sinus rhythm in patients with congestive heart failure.

Key words: Amiodarone, congestive heart failure, atrial fibrillation

Introduction

Pronounced congestive heart failure (CHF) has mortality comparable with worst form of cancer (1). CHF prevalence is 1–2% in general population (2) and it has been dramatically increasing (3), at least because of: 1) number of patients who survive acute myocardial infarction (AMI) has been increased, and substantial myocardial damage leads to CHF (increasing incidence); 2) CHF is much more common in older age, so-called "doubling-by-decade effect" reaching 8–16% among persons aged 75 years and older (1) and average life expectancy has been rising which leads to increased incidence of CHF and 3) management of CHF patients has been better, improving survival that increases prevalence of CHF (3).

One of basic aims of medicine has been also in CHF to prolong life and improve its quality, which can be done with better control of bad prognostic causes. Such one factor is atrial fibrillation (AF), most common chronic dysrhythmia in general, which is important also because it doubles mortality (4). It has been thought that at least 1/5 of CHF patients has AF (4,5). Similar data we obtained from our large series of 340 patients with pulmonary edema, most pronounced type of “left heart” CHF (6).

An interesting difference exists between practice (where we are witnesses of association of CHF and AF every day) and medical publications (which mention CHF usually among less important causes of AF, and sometimes CHF is missing). This, obviously wrong opinion, was corrected by new data from Framingham study (7). Namely, CHF increases chances for AF even 4.5 times (in men) to 5.9 times (in women). It seems that CHF is not only among important factors for AF, but most important one (7)!

The influence of AF upon left ventricle (LV) function can be very pronounced, which was very nicely illustrated by Brill in 1938. y. He stated that "AF may cause CHF without any other heart disease and that following AF cease, recovery may be complete and long lasting" (8).
Negative repercussions of AF in CHF are numerous (9):
- reduction of ejection fraction;
- diastolic dysfunction;
- elevation of filling pressure;
- increase in end-systolic volume;
- reduction of cardiac output;
- elevation of arterial pressure;
- elevation of systemic vascular resistance;
- reduction of contractile reserve;
- increase in plasma levels of atrial natriuretic peptide, epinephrine, norepinephrine and aldosterone;
- loss of myocytes with reactive cellular hypertrophy.

Pulmonary congestion, one of notorious CHF signs, arises due to retrograde transmission of elevated LV pressure. Forceful injection of blood in LV out of left atrium is needed, and exactly this "atrial kick" is lost in AF. Thus, AF directly diminishes LV filling, which is proportional to LV stroke volume (according to Frank Starling's law). In medical literature the significance of tachycardia has been underestimated although tachycardia is more pronounced when AF occurs in CHF. We feel tachycardia underestimated, because tachycardia has been rarely analyzed in light of its profound impact on coronary artery disease (CAD), as the most important cause of CHF! It is out of doubt that the abnormality is more pronounced in patients with CAD as ground cause of CHF, because tachycardia in AF worsens both CHF per se (by decreasing LV filling time, and LV filling is already impaired by elevated LV pressure and by absence of atrial kick) and CAD by itself (by tachycardia -induced increased oxygen consumption, as well as tachycardia - induced decreased oxygen supply, due to decreased diastole duration). Resulting ischemia cause additional abnormalities in both systolic and diastolic heart function, ventricular dysrhythmias, pain (which further elevates blood catecholamines and worsens both CAD and CHF, causing vitious circle), etc. Reality of before mentioned was confirmed by our finding that ischemia was very common in pulmonary edema (10) and that ischemia was important etiologically, therapeutically and as a marker of worse inhospital prognosis (11).

In available medical chapters and studies one important bad influence of AF on CHF is missing, although it is often to be found in practice. It is AF - induced blood pressure (BP) drop, mostly of systolic BP, which makes us unable to give adequate therapeutic response. Namely, AF decompensates CHF and we would like to increase therapy, but we can not (and often we are obligated to decrease therapy!) due to decreased BP, which forces us to reduce doses of diuretics, ACE inhibitors, nitrates. Furthermore, with AF - induced BP drop, therapy of AF becomes more difficult, because hypotension is additional (together with con-}

gestion) contraindication for beta blockers, verapamil and diltiazem. Thus, AF-induced BP drop worsens both CHF and AF, decreasing probability for conversion in sinus rhythm and increasing risk for thromboembolic complications, both venous and arterial. Situation is worse in patients where CAD is dominant cause of CHF, because we must decrease the dose of nitrates, too. In addition, hypotension by itself may diminish perfusion of the heart, CNS, legs, etc. that can be seen often.

Aim of the study is twofold: to point out data from medical publications concerning proper choice of antiarrhythmics for conversion of paroxysmal AF in CHF, as well as to present our own experience concerning this important clinical problem, because extensive publications on this topic is missing.

**Patients and Methods**

We considered AF lasting less than 48h for paroxysmal. There were 20 patients (11 men and 9 women, average age 69.4 ± 5.4y.), hospitalized due to pronounced decompensation of CHF from 1996 on. All patients were in NYHA class III-IV, ejection fraction < 40%, dilated left ventricle (LVEDD = 61.2 ± 3.7 mm) and left atrium (46.4 ± 2.9 mm), but free of acute coronary syndrome and hypokalemia. CAD and hypertension were dominant etiological factors, and almost half patients had diabetes mellitus.

Loading doses of amiodarone were applied, usually 4–6 × 200 mg/24h for a few days, and then 3–4 × 200 mg until conversion to sinus rhythm. The drug was administered sublingually for approx. 1 week in order to achieve its effect faster (12). Ventricular rate was reduced to around 80–100/min. as soon as possible (lower if CAD is etiologically dominant, higher with greater LV dysfunction, to allow heart rate to compensate for decreased stroke volume). Following stabilization of clinical course, we targeted lower ventricular rate (i.e. 60/min) to convert AF.

As thromboembolic risk has been considered low for the first 24–48h of AF duration, anticoagulant therapy for 3–4 weeks was not indicated. We used warfarin overlapped for a few days with low molecular weight heparin (LMWH) Nadroparin (Fraxarin) (13-14). Fraxarin was given s.c. which was much more comfortable for patients than 24 h infusion, that represents volume load (relative contraindication in CHF). Fraxarin was abandoned when INR reechoed 2 (14). Much attention was paid to contraindications for antithrombotic drugs, with individual approach to perceived risk and benefit. Thus, all patients had ranitidine for prevention. All CAD patients had also aspirin 100–150 mg daily all the time. Other medications were used, of course: loop diuretic with spironolactone / K+ supplement, ACE inhibitor, nitrate /molsidomine, digitalis, aminophylline, often tranquilizer, rarely dopamine/ dobutamine.
Results

At time of discharge, 18 patients were in sinus rhythm (90%). One month following discharge one patient more normalized his heart rhythm, making total of 19 patients (95%).

Average time to conversion was 6.1 ± 3.8 days.

In a few patients cardioversion was surprising, because of large LV and left atrium, as well as low EF.

Reduction of ventricular rate was essential: with the whole therapy it dropped from 134.8 ± 13.0 to 82.2 ± 11.3 (p < 0.0001) after 3 days of therapy.

In patients who failed to achieve sinus rhythm, RR intervals become more similar in duration, which accompanied ventricular rate reduction and had positive influence on clinical course.

Several unwanted effects were observed: frequent widening of QTc interval (without ventricular tachycardia type torsade), 4 patients with AV block of I degree (max PQ = 0.28s), which forced us to reduce amiodarone dose. At first time amiodarone unwanted effects watching was focused to ECG abnormalities and hepatotoxicity, and later also others (thyroid gland, lungs, eyes, etc.). Hepatic lesion were expected not only because they may be idiosyncratic, but also due to frequent enlarged liver, found in almost all patients, which might be eventually predisposing factor. In addition such patients often have many medications, which further increased probability for amiodarone toxicity. Despite logical reasons for such expectations, we did not notice hepatotoxicity. On the other hand, we had difficulties to keep INR values 2–3 because amiodarone influenced frequently effect of warfarin. Although we made frequent measurements of INR, 3 patients had INR up to 5, but without manifest bleeding. Such variations have been one of many reasons for us to consider it wise to overlap warfarin with LMWH (and not with standard heparin) in patients with high thrombotic risk (13,14).

Discussion

Hemodynamic and thrombophyllic complications which in CHF become more frequent with AF have important repercussions for morbidity and mortality. From SPAF III study we know that CHF increases possibility for CVA in AF (15). This suggests that CHF make AF worse, not only vice versa (16). In pronounced CHF annual risk for stroke is approx. 16% (4).

AF is bad prognostic sign in CHF, as suggested by large trials (i.e. SOLVD, which founded excess in mortality in CHF with AF (CHF with AF 13.1 vs CHF without AF 8.2; p < 0.001) (5). Definite proof is that conversion to sinus rhythm improved prognosis in CHF patients in CHF-STAT study (17).

To patients with hemodynamic compromise best choice (but, to our sorry, not rarely only temporarily solution is electrocardioversion under heparinization. In CHF patients without obvious life threatening condition (and most of our CHF patients are not in such danger immediately), attempt to medicament cardioversion is usually preferred. The choice of antiarrhythmic for this purpose is very important, and we think it should be amiodarone, because:

1) amiodarone is safe in CHF (18,19) and only amiodarone and beta blockers out of many antiarrhythmics are capable of reducing dysrhythmic death in CHF (19,20), by decrease of ventricular tachycardia & fibrillation (21), that cause half cardiogenic mortality in CHF (19);
2) among drugs that are successful in cardioversion of AF, amiodarone has mildest direct negative inotropic action, and in CHF patients amiodarone increases EF, as a rule (19);
3) Amiodarone is one of the most effective drugs in conversion of persistent AF in sinus rhythm (22);
4) amiodarone - induced conversion may take place even a few months after beginning of amiodarone therapy, even in patients in whom we do not expect it (because of long lasting AF, very enlarged LA, poor LV function, etc.) (22);
5) other antiarrhythmics for cardioversion have worse safety profile (19,21,23,24): propafenone has more pronounced negative and proarhythmic effect (especially in CHF, as well as CAD, which is most frequent cause of CHF); quinidine is less efficacious and safe (25,26) and can increase mortality after longer application; sotalol is less efficacious (24);
6) with first class antiarrhythmics (incl. propafenone, and especially quinidine) ventricular rate may get increased (due to vagolytic action) and frequently rate slowing drug must be given together (like beta blocker or verapamil / diltiazem), which have negative inotropic effect (27).

Unlike persistent AF, in CHF with paroxysmal AF there is no need (to our opinion) to perform transesophageal echocardiography - TEE (which is available in limited number of cardiologic centers and is not comfortable for patients) to exclude presence of thrombus in auricula of LA (not visible on routine transthoracic echo examination). Also, it is not obligatory to wait 3–4 weeks of anticoagulant therapy (to "stabilize" thrombus, which eventually might be present in auricula of LA). This is important, because while waiting, patients have worse hemodynamic and clinical condition and AF becomes more difficult to convert (and, if we manage to do it, recovery of LA mechanical function becomes prolonged).

In case of unsuccessful conversion or AF judged to be permanent, amiodarone has still good effect in ventricular rate control in CHF patients (28). Namely, there are many patients with severe CHF, whom we can not stabilize hemodynamically for a longer period of time because of AF with high ventricular rate, which begets decompensation directly (by reducing EF) and/or indirectly (by causing ischaemia that decrease contractility). Digitalis is to the rule insufficient to control ventricular...
rate even at rest, but especially with effort. Other available drugs for this purpose are contraindicated (in decompensated phase): beta blockers, verapamil, diltiazem. Amiodarone is very potent in this situation, provided that it is administered in sufficient dose. It is not rare that amiodarone converts rhythm even in patients considered to have permanent (" incurable") AF. Such an experience we have with R.S., with artificial mitral valve, EF = 25% and severe aortic insufficiency. He was twice refused to cardiac surgery due to high operative risk. His 4 years old AF was classified as permanent. Because of frequent hospitalizations, incl. those due to pulmonary edema, we administered amiodarone for heart rate control, because digitalis alone was absolutely risk. His 4 years old AF was classified as permanent (" incurable") AF. Such an experience we have with R.S., with artificial mitral valve, EF = 25% and severe aortic insufficiency. He was twice refused to cardiac surgery due to high operative risk. His 4 years old AF was classified as permanent. Such an experience we have with R.S., with artificial mitral valve, EF = 25% and severe aortic insufficiency. He was twice refused to cardiac surgery due to high operative risk. His 4 years old AF was classified as permanent.

In patients with CHF and acute coronary syndrome (excluded from this paper) we have very positive experience with amiodarone. We consider it for new indication for amiodarone: slowing heart rate in sinus rhythm in patients with unstable angina (UAP) or acute myocardial infarction (AMI) with pronounced CHF (12). It has been known that sinus tachycardia is not rare in acute coronary syndromes and that it could affect prognosis by increase in myocardial oxygen consumption, causing ischaemia and thus rhythm and contractility abnormalities, necrosis, etc., especially if CHF was already present. "Repetto" of drugs to decrease HR is very limited in UAP and especially in AMI if accompanied by heart failure, having in mind contraindication for negative inotropic medicaments (beta blockers and especially verapamil / diltiazem). In such patients amiodarone (with careful dosage, and due to its multiple actions) (29) is very useful and safe for diminishing heart frequency.

**Conclusion**

1) CHF increases risk for AF app. 5 times, making AF frequent in CHF, capable of increasing both morbidity and mortality, while conversion in sinus rhythm improves such prognosis. Vice versa, CHF in AF increases risk for CVA, suggesting that CHF and AF have bad influence upon each other.

2) Modern approaches confirm our practice for a few years that amiodarone is the drug of choice for medicament conversion of both paroxysmal and persistent AF in CHF.

3) Amiodarone is very useful for ventricular rate control in severe CHF with permanent AF, although it is only mentioned as indication for this purpose.

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**AMIODARON U KONVERZIJI PAROKSIZMALNE ATRIJALNE FIBRILACIJE U SRČANOJ INSUFICIJENCIJI**

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Kratak sadržaj: Kongestivna srčana insuficijencija (SI) je jedan od vodećih uzroka atrijalne fibrilacije (AF), jer oko 5 puta povećava rizik za AF. Približno svaki peti bolesnik sa SI ima i AF, koja pograbišva hemodinamski status, povećavajući i rizik za CVI i mortalitet. Konverzija AF u sinusni ritam donose nemaštu lošu prognozu. Kako važi i obratno, jer SI u AF takođe povećava opasnost od CVI, može se konstatovati da se SI i AF uzajamno znatno pogravišavaju. Kritična analiza publikovanih studija i pregleda sugeriše amiodaron kao lek izbora za konverziju AF u SI, zbog efikasnosti i bezbednosti, uključujući negativno inotropno i proaritmijsko dejstvo. Analizovali smo 20 hospitalizovanih pacijenata sa paroksizmalnom (< 48 h) AF i SI (uglavnom usled koronarnih bolesti i hipertenzije). Amiodaron je primenjen u dozama uvodjenja (800−1200 mg dnevno). Oralna antikoagulantna terapija varfarinom je "preklopljena" sa niskomolekulskim heparinom (Fraxarin), za što je pogodnji od standardnog heparina, prema našem iskustvu. U sinusnom ritmu je pri otpustu bilo 18 bolesnika (90%), sa prosečnim vremenom do konverzije 6.1 ± 3.8 dana. Mesec kasnije se procenat popeo na 95%, jer je još jedan pacijent konvertovan. U svih bolesnika je bila evidentna redukcija frekvencije. Od neželjenih efekata amiodaronu registrowaismo česta proizvodnja QTc intervala (bez ventrikularnih tahikardija tipa torsade), AV blok prvog stepena u 4 bolesnika, a naročito otežano postizanje željenog raspona efikasnosti varfarina, sa rastom INR-a do 3, ali bez manifesnih krvarenja. Na osnovu podataka iz literature i sopstvenog višegodišnjeg iskustva zaključujemo da je amiodaron najbolji izbor za medicamentosu konverziju paroksizmalne atrijalne fibrilacije u sinusni ritam u pacijenata sa srčanom insuficijencijom.

Ključne reči: Amiodaron, atrijalna fibrilacija, srčana insufficijencija

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