Antiarrhythmics in Heart Failure. State of the Art

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The arrhythmias presents in patients with heart failure, results of different functional and structural factors, secondary to neurohormonal, inflammatory and toxic influences, and changes in the geometric and constitutive elements of ventricular wall and its influences on the wall stress and mechanical efficiency of the heart. This changes are favorable in an initial phase to cardiovascular homeostasis, but on the other hand favoring progressive deterioration of ventricular function, hemodynamic strain and changes in the electrophysiologic substrate. These changes are favorable to expression of ventricular and supraventricular arrhythmias, very frequent in patients with heart failure.

The sudden death is responsible of 30 to 50% of the death in patients with heart failure independent of the etiology [1]. With greater frequency secondary to severe ventricular arrhythmia, ventricular monomorphic tachycardia and its progression to ventricular fibrillation and in smaller number of cases secondary to polymorphic ventricular tachycardia or bradyarrhythmia or electromechanical dissociation, the last arrhythmias especially in terminal heart failure. The most stronger and consistent predictor of cardiac and sudden death is the systolic ventricular function. However the proportion of death by arrhythmia is more important in patients with less functional limitation than patients with functional capacity with more deterioration, in these patients increase the proportion of death by heart failure progression [2]. Notwithstanding sudden death is present in more than 30% of the patients with terminal heart failure. One frequent characteristic in patients with heart failure is the high prevalence of isolated ventricular extrasystoles or repetitive or no sustained monomorphic ventricular tachycardia and the atrial fibrillation. The sudden death physiopathology involved the interaction between trigger mechanism [Ectopic ventricular activity] and modulation mechanism [Autonomic nervous system, myocardial ischaemia, heart failure, electrolytic imbalance], factors than modulate the electrophysiologic substrate with dispersion of conduction velocity and duration of refractory period, associated with changes by healing / fibrosis / remodelation, promote development of severe ventricular arrhythmias. This observation promote the consideration of the sudden death prevention by inhibition of ventricular arrhythmias with pharmacologic and no pharmacologic treatment, the last in especial with automatic defibrillator.

In the context of pharmacologic treatment different antiarrhythmics was evaluated in its impact on total mortality and sudden death in heart failure patients. The results of this studies to allow establish than treatment of ventricular extrasystoles and asymptomatic ventricular tachycardia no receiving benefits and inclusive was contraproducent with incidental increase of arrhymtic mortality by pro arrhythmic effect and by promote clinic and hemodynamic deterioration, secondary to inotropic negative action. Observation of partcicular relevance with drugs than block sodium channels [3], but also with drugs with action in block potassium channels. Dronedarone an no yodated derivate of amiodarone, increased the mortality in heart failure patients. Sotalol, dofelitide and azimilide, without frank benefit in the survival [4,5]

An greater impact in the sudden death reduction is observable with drugs with action than reduce the neurohormonal activity, by angiotensin conversion enzime inhibition or angiotensin receptor AT1 antagonist, or by inhibition of the sympathetic activity with beta blockers [6]. In especial beta blockers have greater efficacy in reduction of the sudden death, total mortality and in diminution of the heart failure progression. An additional utility action of the beta blockers is increase in greater grade the ventricular function with increase of the parameters of systolic function. This benefit is not extensive to all beta blockers, not indicated drugs with intrinsic sympathetic activity or sympathetectic lityc action on central nervous system, both effects increase the mortality. In this pharmacologic group three drugs have comparable efficacy: Metoprolol succinate, carvedilol and bisoprolol. This favorable effect is secondary a its property of block receptor b1, independent at its selectivity, or vasodilator or antioxidant action concomitant [7]. The aldosterone antagonists reduce the total mortality, in particular by reduction of sudden death in patients with functional class III-IV NYHA and in patients with...
myocardial infarction with expulsion fraction < 35%, with ventricular failure or diabetics. Important observation is the reduction in mortality than is additional to the diminution of mortality by angiotensin conversion enzyme inhibition and beta blockers drugs [8].

The more important decision in patients with ventricular arrhythmia and heart failure is identification of patients with increase potential risk of sudden death. In general patients with preserved ventricular function, ventricular extrasystoles or no sustained ventricular tachycardia asymptomatic, have good prognosis. In contrast patients with deteriorated systolic ventricular function, symptomatic recurrent ventricular tachycardia or resulted from sudden death, in general have worse prognosis. In different studies amiodarone is the only into antiarrhythmic drugs than reduce the mortality. In patients without antecedent of sustained ventricular tachycardia, but elevated risk of sudden death, other studies report reduction of total mortality, but others studies report reduction in arrhythmic death, but no reduction in total mortality. Meta-analysis of studies comparative to placebo or controls without treatment, report 29% reduction of relative risk of sudden death and 13% of total mortality with amiodarone. However other studies placebo comparative, amiodarone had not impact in the sudden death or total mortality, without difference irrespective its efficacy in suppression or not of ventricular extrasystoles or no sustained ventricular tachycardia [9,10]. Sotalol similar to amiodarone is effective in suppression of ventricular arrhythmias, however with more important pro-arrhythmic potential and not frank efficacy in mortality. [11].

In contrast with other antiarrhythmic drugs, amiodarone effect is secondary to more complex electrophysiologic actions, interfere with channels of sodium, potassium and calcium, and also with a and b adrenergic receptors. These actions induce reduction in conduction velocity and automatism. Amiodarone had not significative effect pro-arrhythmic and had an favorable effect on ventricular function [12]. Is effective in ventricular and supraventricular arrhythmias suppression, and prevention of atrial fibrillation vs placebo [2,13] In comparison with other antiarrhythmic drugs, amiodarone reduce mortality and recurrence of ventricular tachycardia or fibrillation. However the question is: This results are secondary to action of amiodarone or result of pro-arrhythmic effect of antiarrhythmic class I [14]. In GESICA study in patients with no ischemic dilated cardiomyopathy, amiodarone promote reduction of sudden death and total mortality [15]. In patients post myocardial infarction with frequent ventricular extrasystoles or no sustained ventricular tachycardia, amiodarone reduced the frequency of ventricular fibrillation or arrhythmic mortality [13]. The EMIAT study analysed the effect of amiodarone in mortality in patients with expulsion fraction ≤40% post myocardial infarction, independent of the presence of ventricular arrhythmias. This study report reduction in arrhythmic mortality but no difference in total or cardiac mortality [16]. Both studies post myocardial infarction report reduction in arrhythmic mortality but no impact in total mortality. In post-hoc analysis of these post myocardial infarction studies, the combination of amiodarone with beta blocker was associated with significative reduction of total and arrhythmic mortality, in comparison with amiodarone or beta blocker alone [17]. In contrast others studies on patients with ischemic and no ischemic cardiomyopathy don’t observed than amiodarone reduce the mortality.[18,19]. The SCD-HeFT study compared amiodarone vs placebo and vs automatic desfibrillator in symptomatic patients with expulsion fraction ≤35%. At 3.8 years the total mortality in placebo group was 29%, with amiodarone 28% and in the group with automatic desfibrillator 22%. Significative reduction of 7.2% in absolute risk between desfibrillator group vs placebo [10].

Different studies report beneficent impact on survival with automatic desfibrillator in comparison with antiarrhythmics drugs. The AVID study in patients with expulsion fraction ≤40% and survivors of symptomatic ventricular tachycardia or ventricular fibrillation, analysed antiarrhythmic therapy comparative to automatic desfibrillator. At 18 month of follow-up the mortality was 24% in the antiarrhythmic group [amiodarone or sotalol] and 16% in defibrillator group [20]. The CIDS study in patients with similar characteristics but with more severe compromise of expulsion fraction ≤35%, analysed amiodarone vs desfibrillator. The total, cardiac and arrhythmic mortality was similar between the two groups at 3 years. At difference in CIDS study a great proportion of patients received treatment with beta blockers. Combination than is factible increment the beneficent impact of amiodarone [21]

However the efficacy of the desfibrillator depend of the correct detection and interpretation of severe ventricular arrhythmias and supraventricular arrhythmias, its correct detection and induction of appropriate shock. The electric shock is frequently painful and induce anxiety and limitation in .live quality, on the other hand reduce the median util life of desfibrillator. Optimal utility of desfibrillatot induce analysis of efficacy and security of antiarrhythmic treatment associated to desfibrillator. In patients with desfibrillator by sustained ventriculat tachycardia or spontaneous or inducible ventricular fibrillation, with expulsion fraction ≤40%, was compared the combination of amiodarone with beta blocker vs betablocker or sotalol alone. The primary objective was analysis of the risk of appropriate or inappropriate.shock. The combination was more favorable in comparison to beta blocker or sotalol alone, without difference between sotalol vs beta blocker [22]. The frequency of appropriate and inappropriate shock was smaller with antiarrhythmic class III, in comparison to placebo, however with sotalol, the deterioration of heart failure was more frequent. When comparative antiarrhythmic class III vs beta blocker, the risk of shock, its frequency and recurrence was smaller with amiodarone, but without difference between sotalol and beta blocker [22]

In the decision to amiodarone be employed, is necessary consider the balance between its efficacy in ventricular arrhythmias prevention or suppression, and its smaller pro-aryrrhythmic effect or potential induction of tosade of pointes, polimorfic ventricular tachycardia [< 0.5%], nevertheless its effect in
prolongation of QT interval. While in the cardiovascular sphere is safe and inclusive with favorable effects on ventricular function, in non cardiovascular sphere amiodarone have serious adverse effects [absolute risk 1% when comparative to placebo], by induction of thyroid dysfunction, hyperthyroidism [0.9%] or hipothyroidism [6%]. Toxicity by lung fibrosis, than someone cases to be able to severe or in occasion to be fatal. Likewise can induce hepatic toxicity [0.6%], and peripheral neuropathy [0.3%] [24]. Severe bradychardia is infrecuent. The permanent suspension of treatment with amiodarone by these and other adverse effects, in different studies is between 15 – 30 % [9,10,23].

In patients with automatic defibrillator, the antiarrhythms can induced modification of the desfibrillation umbral and of the ventricular tachycardia longitude cycle with diminution of heart rate below than the programed frecuency of the defibrillator for arrhytmia identification. In animal and clinic studies antiarrhythics with action on sodium channels [flecainide, propafenone], have variable effects on desfibrillation umbral. Sotalol induce diminution of the umbral, but its effect are also variable. Amiodarone have effects on the celular membrane than ensemble effects of others antiarrhythics, in animal studies increase the fibrillation umbral, similar in someone but no all in clinic studies. The beta blockers have not effect on fibrillation umbral. In this patients group is recomended betablocker in all, with expection by intolerance or contraindication. For addition of amiodarona or substitution by sotalol is important individual consideration and analysis of beneficial and potencial adverse effects.

Bibliografia

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