Angiotensin II Receptor Blocker Add-On Therapy for Low Cardiac Output in Decompensated Heart Failure

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Abstract

Background: During heart failure (HF) decompensation, an intense activation of the renin-angiotensin-aldosterone system occurs; however, the use of angiotensin-converting enzyme inhibitor (ACEI) cannot block it completely. Otherwise, the addition of angiotensin II receptor blocker (ARB) can be useful when the inotropic dependence occurs. We evaluated the efficacy of the ARB-ACEI association on dobutamine withdrawal in advanced decompensated HF.

Objective: To assess the efficacy of association angiotensin receptor blocker - angiotensin converting enzyme inhibitor to withdraw the intravenous inotropic support in decompensated severe heart failure.

Methods: In a case-control study (N = 24), we selected patients admitted at the hospital due to HF that had been using dobutamine for more than 15 days, with one or more unsuccessful drug withdrawal attempts; optimized dose of ACEI and ejection fraction (EF) < 0.45. Then, the patients additionally received ARB (n=12) or not (control, n=12). The outcome was the successful dobutamine withdrawal, evaluated by logistic regression, with a p < 0.05.

Results: The EF was 0.25 and the age was 53 years, with a dobutamine dose of 10.7 μg/kg.min. The successful drug withdrawal was observed in 8 patients from the ARB group (67.7%) and in 2 patients from the control group (16.7%). The odds ratio (OR) was 10.0 (95%CI: 1.4 to 69.3; p = 0.02). The worsening in renal function was similar (ARB group: 42% *vs* control group: 67%; p=0.129).

Conclusion: In this pilot study, the ARB-ACEI association was associated with successful dobutamine withdrawal in advanced decompensated heart failure. The worsening in renal function was similar in both groups. Further studies are necessary to clarify the issue. (Arq Bras Cardiol 2010;94(2): 219-222)

Key Words: Congestive heart failure, prognosis, angiotensin II type 1 receptor blockers.

Introduction

Acute decompensation in heart failure (HF) is a moment that requires specific conducts in order to obtain the best results. The need for inotropic support is not unusual and some patients develop drug dependence. This situation has been scarcely studied and some authors consider it only as a "bridge" to heart transplant or the end of the life[1]. Therefore, it becomes necessary to find options for these patients.

One option would be the decrease in the systemic arterial resistance to allow the withdrawal of the inotropic support. Intravenous vasodilators have been used for this purpose; however, other vasodilation strategies could be useful. The concept of multiple blocking of the renin-angiotensin-aldosterone system (RAAS), i.e., the association between the angiotensin-converting enzyme inhibitor (ACEI) and the angiotensin II receptor blocker (ARB), has been studied at earlier stages of HF; however, it has not been assessed at more advanced stages of the disease.

In HF, the more advanced the disease from a clinical point of view, the more activated is the RAAS. The RAAS pathways are redundant and the angiotensin-converting enzyme (ACE) is responsible for the production of only 11% of angiotensin II[2]. Thus, the ACEI does have the capacity to block most of the production of angiotensin II and the stimulation of the system persists.

On the other hand, in theory, the ARB could interrupt this stimulation, as it competes in the AT1 receptor with both the angiotensin II produced by ACE and the one produced by other enzymes, which results in an increase of angiotensin II[3]. Higher levels of angiotensin II can stimulate the AT2 receptor, of which expression occurring in situations of tissue injury.

Methods

This is a case-control pilot study to evaluate the efficacy of the association between AT1 receptor blocker of angiotensin II and the angiotensin-converting enzyme inhibitor on dobutamine withdrawal in patients with inotropic support dependence caused by acute decompensation of chronic HF.

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We selected patients among those admitted at a tertiary hospital from December 2002 to September 2004. We included patients with inotropic support dependence, defined as a duration ≥ 15 days of dobutamine use or one or more unsuccessful withdrawal attempts, or both. The unsuccessful dobutamine withdrawal was defined as the worsening in apnea or fatigue, marked arterial hypotension, mental confusion and worsening of renal function after the decrease or even withdrawal of the drug infusion.

Other inclusion criteria were: left ventricular ejection fraction (EF) ≤ 0.45[4]; and optimized use of angiotensin-converting enzyme inhibitor, diuretics and digitalis. The etiology of the ventricular dysfunction was not an inclusion criterion.

The exclusion criteria were: systolic arterial pressure ≤ 70 mmHg; serum urea ≥ 200 mg/dL; serum potassium ≥ 6.0 mEq/L; clinically significant aortic stenosis; acute coronary syndrome; myocardial revascularization procedures; and cerebrovascular accident in the two months prior to the study.

In the ARB group, the angiotensin II-receptor blocker was added to the optimized use of the angiotensin-converting enzyme inhibitor, defined as the highest dose tolerated by the patient, with the following target-doses: captopril 150 mg/day, and enalapril 20 mg/day. Ten patients used losartan, initially 25 mg/ day, and later, 25 mg twice a day and 50 mg twice a day (target-dose). Two patients used irbesartan, 75 mg/day, and later, 75 mg twice a day, 150 mg twice a day (target-dose). During these sequences, the systolic arterial pressure was not allowed to decrease below 70 mmHg.

We monitored the renal function through serum measurements of urea, creatinine, sodium and potassium every three days and, if necessary, daily. In patients with serum urea < 50 mg/dL and creatinine < 1.5 mg/dL, we considered the worsening in renal function as levels > 100 mg/dL and 2.5 mg/dL, respectively. In a situation with urea levels > 100 mg/dL and creatinine > 2.5 mg/dL, we considered the worsening in the renal function as the occurrence of at least a two-fold increase in the initial value.

The control group was selected according to the same criteria of inclusion and exclusion with the objective of pairing sex, age, EF, serum sodium and renal function. In this group, the initial moment was considered from the definition of dobutamine dependence (more than 15 days of dobutamine use or one or more attempts to withdraw the vasoactive drug).

The main outcome was the successful withdrawal of dobutamine. The occurrence of death was recorded.

Statistical analysis

The continuous variables were expressed as mean and standard deviation and analyzed through the Student's *t* test. The categorical variables were expressed in numbers and proportions and analyzed through Fisher's exact test or Chi-square test. A p value <0.05 was considered significant (two-tailed).

The variables with a p value < 0.10 were included in the multivariate analysis through the logistic regression method[5], for the calculation of the odds ratio (OR) and the respective 95% confidence interval (95%CI). The survival curves were constructed by the Kaplan-Meier method[6] and compared by the Log-Rank test.[7] These analyses were carried out using the statistical program SAS (Cary, NC, USA).

Ethics

This study was evaluated and approved by the Ethics Committee for Analysis of Research Projects of Hospital das Clinicas of the School of Medicine of the University of Sao Paulo (CAPPesq-HCFMUSP), in accordance to the Helsinki Declaration.

Results

We selected 24 patients, 12 in ARB group and 12 in the control group, aged 53 ± 15 years, with EF = 0.25 ± 0.06; the most frequent etiology was Chagas' disease (54.2%). The patients had been treated with dobutamine for a period of 33.5 ± 21.8 days before the start of the study, at a dose of 10.7 mcg/kg.min. Table 1 shows the basal characteristics according to the group.

The worsening in renal function occurred in 13 (54%) patients: 5 (42%) in the ARB group and 8 (67%) in the control group, with p = 0.219.

The successful dobutamine withdrawal was achieved in 8 (66.7%) patients from the ARB group and in 2 (16.7%) from the control group, with p = 0.013, at the univariate analysis. Successful dobutamine withdrawal was associated with higher serum sodium (p = 0.013) and a tendency towards lower serum creatinine levels (p = 0.059). These variables were analyzed by logistic regression, which identified the use of ARB as an independent variable for the successful dobutamine

Table 1 – Basal characteristics

	ARB Group (n = 12)	Control Group (n = 12)	p
Age, in years, mean (SD)	53.6 (18.8)	52.6 (11.0)	0.789
Males (%)	8 (67)	10 (83)	0.640
LVEF, mean (SD)	0.25 (0.05)	0.26 (0.08)	0.724
Chagas' Disease (%)	6 (50)	7 (58)	0.682
Dobutamine, µg/kg, min, mean (SD)	10.7 (3.5)	10.8 (3.5)	0.948
Duration of dobutamine use, days, mean (SD)	38.7 (25.8)	28.4 (16.6)	0.232
High ACEI dose (%)	6 (50.0%)	5 (41.7%)	
High furosemide dose (%)	4 (33.3%)	2 (16.7%)	
Digitalis (%)	11 (91.7%)	5 (41.7%)	
Serum sodium, mEq/L, mean (SD)	133.4 (3.6)	131.0 (5.3)	0.084
Serum urea, mg/dL, mean (SD)	62.3 (41.2)	89.2 (31.5)	0.136
Serum creatinine, mg/dL mean (SD)	1.5 (0.8)	1.8 (0.4)	0.351

LVEF – Left ventricular ejection fraction; n – number of patients; SD – Standard Deviation; ACEI – angiotensin-converting enzyme inhibitor; High ACEI dose: captopril > 75mg/d or enalapril > 10 mg/d; High furosemide dose: > 80 mg/d orally, or 40 mg/d IV route.

withdrawal, with an OR of 10.0 (95%CI: 1.4 to 69.3; p = 0.02). Sodium and creatinine levels were not associated with the successful drug withdrawal.

The interval between the start of ARB administration and dobutamine withdrawal was 19.4 ± 17.0 days and the losartan dose (n = 10) was 62.5 ± 29.5 mg/day, whereas the irbesartan dose (n = 2) was 300.0 ± 212.1 mg/day.

Fifteen patients of the total sample died: 5 (41.7%) from the ARB and 10 (83.8%) from the control group. In the ARB group, the mortality was 25% among the patients that achieved successful dobutamine withdrawal, whereas it was 75% among those that did not. In the control group, the mortality rate was 90% among those that did not achieve the vasoactive drug withdrawal. The survival curves are shown in Figure 1. After a two-month follow-up, the mortality was 56% (95%CI: 34.8% to 78.4%).

Discussion

Our results demonstrated that the ARB-ACEI association was related to a higher probability of dobutamine withdrawal in patients with decompensated heart failure.

The Val-HeFT study demonstrated that the ARB-ACEI association reduced the duration of hospitalization; however, it did not alter the mortality[8]. Differently, the CHARM-ADDED study found a decrease in both hospitalization duration and cardiovascular mortality, although it did not show a decrease in total mortality[9]. However, both studies evaluated patients with moderate HF, with a mortality of 19.5% in 23 months at the Val-HeFT and 31% in 41 months in the CHARM-ADDED study. Our two-month mortality of 56.6% shows the HF severity in our sample, which is also compatible with the situation of dobutamine dependence.

Binkley et al[10] studied vasodilatation with hydralazine for dobutamine withdrawal in 5 patients whose EF was 0.12; the dobutamine dose was 13.4 mcg/kg.min. The hydralazine use improved the cardiac index, the pulmonary capillary pressure and the peripheral vascular resistance, which allowed the dobutamine weaning in all these patients[10].

During the HF decompensation, the aim is the hemodynamic improvement, with the increase in the cardiac index, reduction in the ventricular filling pressure and the peripheral vascular resistance. This objective must be the priority on the process of cardiac remodeling, as it has mid-term and long-term influence.

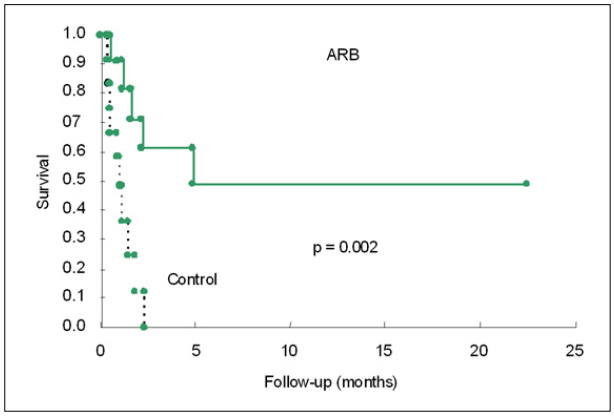

Figure 1 – Survival curve according to the use or not of angiotensin II receptor blocker (ARB).

In decompensated HF, there is controversy regarding the choice the choice between inotropic and vasodilatation agents. Probably, in some situations, such as dobutamine dependence, both are necessary. The vasodilatation treatment is sodium nitroprussiate, I.V.; however, its use is limited in patients already with arterial hypotension.

The acute hemodynamic effects of the ARB have been described. Baruch and cols. found a decrease in the pulmonary capillary pressure and a tendency toward a decrease in the peripheral vascular resistance 6 to 12 hours after the administration of valsartan in patients without ACEI[11]. The hemodynamic improvement occurs two hours after the ingestion of losartan, with an 18% decrease in the peripheral vascular resistance and a 25% increase in the cardiac index[12]. These hemodynamic effects are enhanced after weeks of ARB use[13].

The production of angiotensin II by non-ACE enzymes, such as chimase, catelepsin and kallikrein, make the full vasodilatation through the ACE inhibition unlikely[2,14]. The multiple blocking of the RAAS can lead to a higher vasodilatation in situations of higher peripheral resistance, such as the decompensation of HF. This additional vasodilatation can allow the dobutamine withdrawal in patients with chronic low cardiac output that are dependent on inotropic support.

The herein-proposed model of multiple vasodilatation seems to be appropriate, considering that an intense activation of the RAAS occurs during the HF decompensation, with redundant pathways.

In the present study, the probability of dobutamine withdrawal was ten-fold higher with the use of the ARB-ACEI association than with the isolated full dose of ACEI and most frequent evolution in the control group was the occurrence of death.

For these reasons, we consider the ARB-ACEI association a good option for inotropic support dependence. In our patients, the worsening in renal function was frequent, probably due to the HF severity, but it was not different between the groups.

The importance of the present study is to demonstrate the significant clinical improvement and indicate a direction for the treatment of dobutamine dependence in decompensated heart failure.

Study limitations

The case-control design with a relatively small sample is not strong enough evidence to indicate the routine use of the ARB-ACEI association in a situation of inotropic support dependence. The most frequent etiology was Chagas' disease, which limits the generalization of findings, mainly in other countries. The outcome used in the study, the successful dobutamine withdrawal, is a clinically relevant event; however, the hemodynamic situation was not objectively evaluated. The worsening in the renal function

was similar between the two groups; nevertheless, the possibility of a type II error cannot be ruled out, due to the sample size; even so, the renal dysfunction was more frequent in the control group.

Conclusions

In this pilot study, the ARB-ACEI association was related to the successful dobutamine withdrawal in patients with decompensated HF. The worsening in renal function was not more frequent. Randomized studies are necessary to clarify the issue.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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