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# Chronic utilization of agents acting on the renin-angiotensin system and intraoperative arterial pressure

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**Abstract. – BACKGROUND: There has been concern that taking agents acting on the renin-angiotensin system (ARAS) in surgery day, may predispose patients to higher risk of intraoperative hypotension during surgery. Therefore, the European Society of Cardiology and the European Society of Anesthesiology recommend transient discontinuation of ARAS before non-cardiac surgery in hypertensive patients. As the existent evidence is limited, this recommendation remains debated.**

**AIM: The objectives of the study were to evaluate the effects of ARAS chronic utilization on intraoperative arterial pressure.**

**PATIENTS AND METHODS: This historical cohort consisted in recruitment of surgery patients over 12 months, at "Cova da Beira Hospital Center". The data were gathered from an interview to the patient and by postoperative review of the medical record.**

**RESULTS: The study consisted of 756 patients. Of those, 589 did not take antihypertensive medication and 176 were taking chronic ARAS.**

**In univariate analysis, only the appearance of intraoperative hypertension was significantly greater in ARAS group. In logistic regression analysis, age, diabetes mellitus and taking ARAS were the only significant risk factors to the appearance of intraoperative hypertension.**

**In ARAS group, 123 patients stopped the ARA before surgery and 53 continued it until the surgery day. The frequency of the two outcomes did not differ between the two groups.**

**CONCLUSIONS: In our study hypotension episodes during non-cardiac surgery could not be attributed to ARAS chronic utilization and taking ARAS on surgery morning when compared with withdrawal was not associated with hypotension episodes.**

*Key Words:*
Angiotensin-converting enzyme inhibitors, Angiotensin II antagonists, Intraoperative arterial pressure, Surgery.

## Introduction

Agents acting on renin-angiotensin system (ARAS) are established as safe and effective therapeutic in hypertension, namely in patients with concomitant diabetes mellitus or compromised left ventricular function[1]. As result a large proportion of patients presenting for elective surgery are taking ARAS to treat some form of cardiovascular diseases. Several reports suggest that taking ARAS in surgery day may predispose patients to higher risk of intraoperative hypotension during surgery[2-6]. Intraoperative hypotension has been associated with postoperative cardiovascular events, renal dysfunction and mortality[7-12]. Therefore, the European Society of Cardiology and the European Society of Anesthesiology recommend transient discontinuation of ARAS before non-cardiac surgery in hypertensive patients[13]. As there is limited evidence and some data suggest this recommendation may result in hypertension in the postoperative period, this subject remains debated[14]. However, the same guidelines recommend that ARAS be continued during non-cardiac surgery in stable patients with left ventricular systolic dysfunction. Further perioperative studies are critically needed to evaluate the effects of ARAS chronic utilization in arterial pressure.

The objectives of this study were to evaluate the effects of chronic utilization of ARAS on arterial pressure during the operative period.

## Patients and Methods

This historical cohort was approved by the Ethics Committee of Cova da Beira Hospital Center (CBHC) that provided a written consent, to be requested to each patient. The written con-

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sent was presented to the patient before the interview. The records of patients that refused to participate in study could not be consulted. Therefore, only the patients that gave written consent were included in the study.

Patients were selected over 12 months, between September 2008 and September 2009 at CBHC. Eligible patients included those having at least 18 years old, an anesthesia consultation, proposed for elective general, orthopedic, gynecologic, urologic, neurologic, maxillofacial, ear, nose and throat (ENT) and plastic surgery. The exclusion criteria were ambulatory surgery, local anaesthesia, patients taking other cardiovascular drugs than ARAS, not speaking portuguese or any condition that compromised patients ability to communicate and/or understanding and the absence of written consent.

Patients were interviewed before anesthesia consultation by a member of the research team, to ensure that criteria for enrollment were met and to query regarding chronic medication. Chronic medication was defined as the medication which the patient was taking for more than 2 weeks before the surgery.

All other data were gathered from postoperative review of the medical record. Three separate sets of data were collected: demographic characteristics, chronic medication use, the clinical information.

The patient demographics and chronic medication use was asked in the interview and confirmed in medical record. These include the age, sex, weight, and height, the name of each chronic medication, route administration and stop and start dates.

The clinical information included the American Society of Anaesthesiologists physical status classification (ASA), surgery service, occupation time in surgery, type of anaesthesia and drugs given in perioperative period. Clinical history data (previous surgeries, chronic diseases) and exam pre-operatory results were not possible to access due to administrative restrictions. As such it was not possible to separate patients taking ARAS for hypertension from those taking them because of left ventricular systolic dysfunction.

The outcomes hypertension and hypotension were defined by threshold values with concomitant administration of antihypertensives or vasopressors drugs. The limit threshold was systolic blood pressure value more than 160 mm Hg for hypertension, and systolic blood pressure value less than 85 mm Hg for hypotension.

In the analysis, first we compared patients that take no antihypertensive medication with patients on ARAS. Antihypertensive medication includes diuretics, beta blocking agents, calcium channel blockers, antiadrenergic agents and ARAS. The ARAS includes angiotensin-converting enzyme inhibitors in plain (the pill only had the angiotensin-converting enzyme inhibitor) and in combination (the pill had two drugs, the angiotensin-converting enzyme inhibitor and a diuretic or a calcium channel blocker), angiotensin II antagonist in plain and in combination (diuretic or calcium channel blocker). In a second approach, the group of patients on chronic ARAS were divided in two, patients that withdrawal ARAS in the days before or in the surgery day (ARAS stop group) and the group that took ARAS until the day of surgery (ARAS continue group), inclusively (this includes the patients in which ARAS were replaced for a drug of the same subtherapeutic group).

On the basis of a previous report[4], it was assumed that 67% ARAS continue group would have at least one hypotension episode during surgery. To detect a 30% difference in frequency of hypotension episode during surgery between ARAS continue group versus ARAS stop group, with a power of 80% (two tailed $\alpha = 0.05$), the sample size should have a minimum of 25 patients per group.

The continuous variables were initially assessed for normality. Variables found to be normally distributed were compared using Student *t*-test, while non-normally distributed variables were compared using Mann-Whitney U tests. Categorical variables were compared using chi-square tests. All associations found to be significant in the univariate analysis ($p < 0.05$) were entered into a forward stepwise logistic regression analysis to identify predictors of outcomes. A $p$ value cutoff of 0.05 for entry and 0.10 for exit was used. Results from the multivariate model have been reported as Odd's Ratios (OR) with 95% Confidence Interval (CI). A two-sided $p$ value of 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS Version 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

The study consisted of 765 patients. Of those, 589 did not take antihypertensive medication and 176 were taking chronic ARAS (Figure 1).

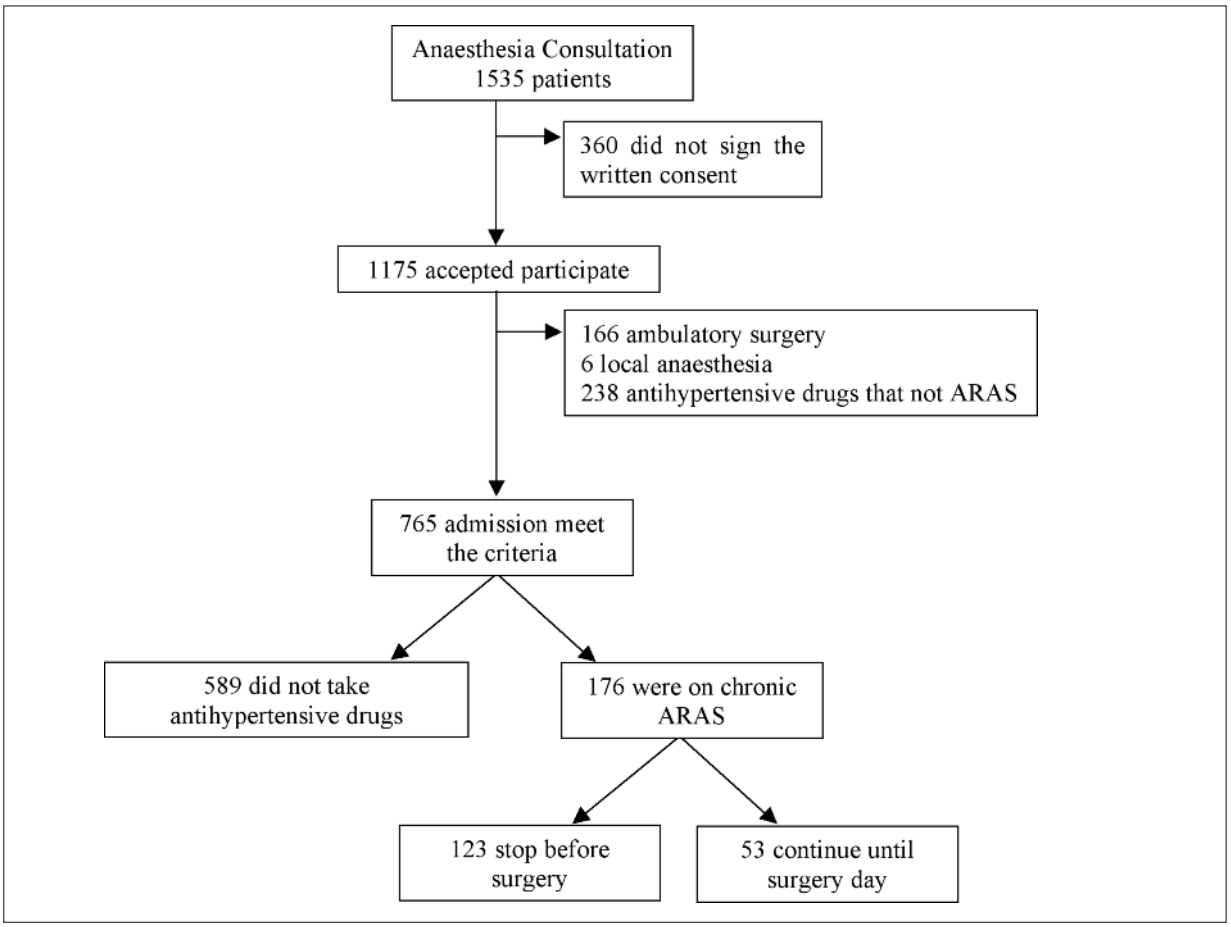


**Figure 1.** Flow diagram of the patients enrolled in the study.

The medical records had some missing data, namely 15.7% did not have ASA status classification, 0.8% did not have type of anaesthesia, in 5.0% the occupation time was not registered and 0.7% did not have the day in which ARAS were suspended.

In groups, (no antihypertensive medication and chronic ARAS) there were more female patients. Chronic ARAS group had a mean age of 13 years older and more patients with diabetes requiring therapy. As in the distribution of patients in the ASA status classification it is not possible to apply Chi-square test, we decided to aggregate ASA I with ASA II (ASA I/II) and ASA III with ASA IV (ASA III/IV). Chronic ARAS group had more patients with ASA III/IV classification ($p = 0.000$). The number of patients submitted to general or regional anaesthesia was similar in the two groups. In chronic ARAS group there is a higher proportion having surgery more than 121 minutes with a statistically significant difference ($p = 0.020$) (Table I).

There was an increased frequency of the two outcomes evaluated in Chronic ARAS group. However, in univariate analysis, only the frequency of intraoperative hypertension was significantly greater in chronic ARAS group (Table I). In logistic regression analysis of the risk factors to appearance of intraoperative hypertension, only age ($p = 0.000$, OR 1.05, 95% CI 1.03-1.08), diabetes ($p = 0.034$, OR 2.45, 95% CI 1.07-5.60) and chronic ARAS use ($p = 0.038$, OR 1.91, 95% CI 1.04-3.50) were statistically significant. The ASA status ($p = 0.283$) and the occupation time ($p = 0.290$) were not associated to intraoperative hypertension in logistic regression.

In chronic ARAS group, 123 (77.4%) patients stopped ARAS before surgery and 53 (30.1%) continue the medication until surgery day, inclusively. The two groups were comparable in patient characteristics (Table II). The frequency of the two outcomes did not differ between the two groups.

The appearance of hypertension was significantly higher in ARAS stop group ($p = 0.000$)

**Table I.** Patient characteristics by groups no antihypertensive medication and chronic ARAS.

| Characteristic | Patients number (%) | | |
|---|---|---|---|
| | No antihypertensive medication (n = 563) | Chronic ARAS (n = 176) | $\chi^2$ (p) |
| Sex | | | |
| Female | 373 (63.3) | 118 (67.0) | 0.367 |
| Male | 216 (36.7) | 58 (33.0) | |
| Age (years) | | | |
| Mean (standard deviation) | 49.58 (14.76) | 62.95 (11.11) | 0.000 |
| Diabetes requiring therapy | 19 (3.2) | 27 (15.3) | 0.000 |
| ASA Status | | | |
| I/II | 449 (91.1) | 114 (75.0) | 0.000 |
| III/IV | 44 (8.9) | 38 (25.0) | |
| Type of Anesthesia | | | |
| General | 468 (80.1) | 139 (79.4) | 0.837 |
| Regional | 116 (19.9) | 36 (20.6) | |
| Occupation Time (minutes) | | | |
| 1-120 | 365 (64.8) | 90 (54.9) | 0.020 |
| ≥ 121 | 198 (35.2) | 74 (45.1) | |
| Outcomes | | | |
| Hypertension | 38 (6.5) | 35 (19.9) | 0.000 |
| Hypotension | 34 (5.8) | 14 (8.0) | 0.295 |

and ARAS continue group ($p$ = 0.001), when compared with no antihypertensive medication group. Nevertheless the frequency of hypotension was similar between no antihypertensive medication and chronic ARAS either continuing ($p$ = 0.544) or stopping it ($p$ = 0.323).

Of the 123 patients that withdrawal the medication, 96 (78.0%) stopped in the surgery day, 21 (17.0%) stopped one day before de surgery, 3 (2.4%) stopped two or more days before the surgery and data is missing in 3 (2.4%) patients. There was no difference in the frequency of two

**Table II.** Patients characteristics by chronic ARAS management.

| Characteristic | ARAS – number of patients (%) | | |
|---|---|---|---|
| | Stop (n = 123) | Continue (n = 53) | $\chi^2$ (p) |
| Sex | | | |
| Female | 77 (62.6) | 41 (77.4) | 0.056 |
| Male | 46 (37.4) | 12 (22.6) | |
| Age (years) | | | |
| Mean (standard deviation) | 3.07 (11.89) | 62.70 (9.150) | 0.825 |
| Diabetes requiring therapy | 18 (14.6) | 9 (17.0) | 0.692 |
| ASA Status | | | |
| I/II | 82 (75.9) | 32 (72.7) | 0.680 |
| III/IV | 26 (24.1) | 12 (27.3) | |
| Type of Anesthesia | | | |
| General | 98 (80.3) | 41 (77.4) | 0.655 |
| Regional | 24 (19.7) | 12 (22.6) | |
| Occupation Time (minutes) | | | |
| 1-120 | 59 (52.7) | 31 (59.6) | 0.406 |
| ≥ 121 | 53 (47.3) | 21 (40.4) | |
| ARAS Classes | | | |
| ARAS in plain | 57 (67.9) | 27 (32.1) | 0.575 |
| ARAS in combination | 66 (71.7) | 26 (28.3) | |
| Cardiac Adverse Event | | | |
| Hypertension | 24 (19.5) | 11 (20.8) | 0.850 |
| Hypotension | 10 (8.1) | 4 (7.5) | 1.000 |

outcomes between patients who withdrawn ARAS in surgery day and patients that stopped ARAS one or more days before surgery (Table III).

## Discussion

There has been concern that taking ARAS in surgery day may predispose patients to higher risk of intraoperative hypotension during non cardiac surgery. The present study found no evidence to support this risk.

In the present study patients taking ARAS had more risk of intraoperative hypertension, than the patients taking no antihypertensive medication, when adjusted to confounders. This result can be expected, because ARAS are a therapy of choice in hypertensive disease. However, there is no difference in the occurrence of intraoperative hypotension between the two groups.

There was no statistically significant difference in the frequency of hypertension and hypotension between withdrawing and continuing chronic ARAS in perioperative period. Also, there was no significant difference in the occurrence of the two outcomes between patients that stop medication in surgery day and patients that stop the medication one or more days before surgery.

The patients that were taking beta-blockers and antiadrenergics drugs were excluded from the study, because beta-blockers may predispose patients to higher risk of intraoperative hypotension[15-16].

The management of the different antihypertensive drugs was not equal in all patients, which is an additional confounder. For this reason only the patients taking ARAS in combination (the same pill had the two drugs) were included in study. We not restrict the study to the patients that were taking only ARAS in plain, because the majority of patients (52.3%) were taking ARAS in combination.

Existing studies comparing ARAS users with ARAS non users, concluded that the number of patients requiring vasopressor was not significant different between the two groups[15,17]. In one study, the patients took ARAS in surgery morning and in the other patients did not take the ARAS in surgery morning[15,17]. These results are consistent with ours, although they did not exclude patients taking beta-blockers. However, a meta-analysis suggested that patients receiving an immediate preoperative ARAS were more likely (relative risk 1.50, 95% CI 1.15-1.96) to develop hypotension requiring vasopressors[18]. This meta-analysis is composed by five small studies with a considerable variation in design quality from study to study and it should be noted that the lower limit of 95% confidence interval for the OR approached 1, indicating that this was not a pronounced effect.

The lack of difference between the groups taking no antihypertensive medication and taking ARAS and between the groups withdrawing vs continuing chronic ARAS in risk of intraoperative hypotension is biologically plausible. The potent hypotensive effects of anesthetic, intraoperative analgesic agents and the surgery predominate relatively to the administration of ARAS.

The present study has several limitations. First, the data were collected as part of the medical record, not a specific study protocol data collection process. As such it was not possible to evaluate the indication (hypertension or left ventricular systolic dysfunction) for which ARAS were prescribed. Moreover, some anesthesiologists use vasopressor or fluid boluses before hypotension occurs, which can further decrease the frequency of hypotension[6].

## Conclusions

The European Society of Cardiology and the European Society of Anaesthesiology recommend transient discontinuation of ARAS before non-cardiac surgery in hypertensive patients, to reduce the risk of severe hypotension under anesthesia associated to perioperative use of ARAS. However, the same guidelines recommend their maintenance during non-cardiac surgery in stable patients with left ventricular

**Table III.** Outcomes by ARAS suspension day.

| | Suspension day – number of patients (%) | | |
|---|---|---|---|
| | Day surgery | ≥ 1 day before surgery | $\chi^2$ ($p$) |
| Hypertension | 20 (20.8) | 4 (16.7) | 0.780 |
| Hypotension | 8 (8.3) | 1 (4.2) | 0.685 |

systolic dysfunction[13]. As ARAS preserve organ function and may prevent events related to myocardial ischemia and left ventricular dysfunction, independently of the blood pressure lowering effect, further larger scale prospective studies are critically needed to support ARAS discontinuation in hypertensive patients before surgery.

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