BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. **21**: 121–128 (2000)

Influence of Acebutolol and Metoprolol on Cardiac Output and Regional Blood Flow in Rats

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ABSTRACT: Beta-adrenoceptor blocking drugs are widely used as effective antihypertensive and antianginal agents. We have determined the effect of β-blockade in the rat to ascertain whether there are differences between metoprolol (MET) and acebutolol (AC) with respect to regional blood flow (RBF). Both AC and MET were administered as a single or multiple intravenous (iv) doses in Sprague–Dawley rats. Microspheres labelled with ^{85}Sr and ^{141}Ce were used to measure cardiac output (CO) and RBF before and after drug administration. CO and RBF were measured 1 and 10 min after the iv administration of AC (30 mg/kg) and MET (10 mg/kg). After acute administration of MET, CO decreased by 65% and 31% after 1 and 10 min measurements, respectively. These values were 54% and 28% for AC as compared with baseline values. After chronic administration of either AC or MET, however, there were no significant reductions in CO as compared with saline. Both MET and AC significantly reduced RBF in most organs either after 1 or 10 min measurements when compared with the baseline values. It is concluded that both AC and MET reduced CO and RBF after acute administration. The CO and RBF however, returned to normal after chronic administration. Copyright © 2000 John Wiley & Sons, Ltd.

Key words: acebutolol; cardiac output; metoprolol; regional blood flow

Introduction

Beta-adrenergic receptor blocking drugs are now widely prescribed for both angina and hypertension. Although these drugs are equally effective in reducing blood pressure, they are different in ancillary properties such as affinity for β_1 and β_2 adrenoceptors, bioavailability, lipid solubility and partial agonist activity or intrinsic sympathomimetic activity (ISA, [1]). These ancillary properties, however, may be important with regard to safety, side effects, and the haemodynamic effects of these drugs.

In particular, acebutolol (AC) and metoprolol (MET) are β-blockers whose properties are similar in most aspects. Both AC and MET are cardioselective, exhibit low binding to plasma protein possess a Pk_a, of 9.7 and an oral bioavailability of approximately 40–50%. MET is eliminated from the body by hepatic metabolism. AC however, is eliminated by both renal clearance and hepatic metabolism. Although these agents are similar in their pharmacokinetic properties and in their pharmacological activity in lowering the blood pressure they differ with regard to some ancillary properties such as ISA. While AC possesses some degree of ISA, MET is devoid of this property [2].

The presence of ISA in β-blockers modifies the pharmacological effects of these agents. It has been reported that cardiac haemodynamics and the effects on peripheral circulation vary according to the extent of ISA possessed by β-blockers [3]. Drugs with ISA cause less decrease in heart

Abbreviations: AC, acebutolol; ANOVA, analysis of variance; CO, cardiac output; ISA, intrinsic sympthomymetic activity; MET, metoprolol; RBF, regional blood flow.

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Received 17 June 1999
Accepted 8 June 2000

rate and cardiac output (CO) at rest than those without it. Furthermore, the effects of ISA may be different after acute administration of drugs as it compared with chronic administration [4,5].

The aim of the present study was to investigate the acute and chronic haemodynamic effects of AC (which has a moderate degree of ISA) and MET, (which is devoid of ISA) in the rat, in particular to demonstrate CO and regional blood flow (RBF) changes induced by these two β-blockers with different degrees of ISA. To determine values of CO and RBF the radioactive microsphere method was used.

Materials and Methods

Chemicals

AC hydrochloride and MET tartrate were obtained from Sigma Chemical Company (IL, USA). Radio-labelled microspheres (^{141}Ce and ^{85}Sr) with a diameter of 15 μm were purchased from Dupont NEN (Wilmington, DE, USA) and dissolved in physiological saline containing 0.01% Tween 80. All other chemicals and reagents were analytical grade.

Surgery and Animal Maintenance

Thirty six male Sprague–Dawley rats weighing between 310–360 g were kept on a light–dark cycle of 12 h at a room temperature of 25°C. Under general anaesthesia with pentobarbital administered via the peritoneal route, the animals were catheterized with silastic tubing (0.025 in. i.d. × 0.037 in. o.d.; Dow Corning, Midland, MI, USA) in the right jugular vein for the purpose of drug administration. A cannula, the top of which was tapered to reduce damage to cardiac tissue, was inserted through the right carotid artery into the left ventricle. The femoral artery was cannulated to allow for taking reference blood samples; this could be consistently accomplished within 10 min.

Dosing and Sample Collection

The CO and RBF were measured with the microsphere method. The cannula for the femoral artery was connected to a heparinized syringe (1.0 mL) fixed in a withdrawal pump (syringe infusion pump, Harvard Apparatus, Millis, MA, USA). Microspheres labelled with either ^{141}Ce or ^{85}Sr were suspended in 0.5 mL of normal saline and were injected (with 2 μci of radioactivity) into the left ventricle over an interval of 30 s. This was followed by 0.4 mL physiological saline to flush in any microspheres remaining in the cannula. Ten seconds before the administration of microspheres, reference blood sample withdrawal was begun from the femoral artery at the rate of 0.26 mL/min. The microspheres were injected and flushed with 0.4 mL of physiological saline. The withdrawal of reference blood sample was stopped after approximately 2 min. Before the injection of drug or saline, microspheres labelled with one or other of the two nucleotdes were administered randomly as described above. Again, 1 min and 10 min after the administration of either drug or saline the microspheres labelled with the other nucleotides were administered. Rat was sacrificed by intravenous (iv) administration of pentobarbital (50 mg/kg). The heart, lung, liver, stomach, spleen, muscle, kidneys and skin were sampled, blotted and weighed. The radioactivities were measured by a gamma counter (Miniaxi γ Canberra Packard, Canada).

For evaluating the long term effects of AC or MET, rats were administered either drugs or saline orally every 8 h for 4 days. AC [6] and MET [7] are rapidly absorbed after oral administration in rat. Thus, the last dose administered was allowed to be absorbed for 10 min. Following this, each rat was anaesthetized, cannulated as described perviously and microspheres labelled with different nuclides were administered randomly. Again, the rats were sacrificed by iv administration of pentobarbital. Different organs were sampled, blotted, weighed and radioactivity in each organ was measured as described above.

CO and RBF Measurements

Tissue activity of each isotope was calculated after subtraction of the background and the overlapping isotope activity by conventional stripping procedures [8]. For computation of the counts injected into the left ventricle, the initial

activities in the vial from which the microspheres were aspirated were counted. The CO and the RBF were computed as follows:

$$\text{CO (mL/min/kg)} = \frac{\text{Counts injected in left ventricle} * \text{blood withdrawal flow (mL/min)}}{\text{Counts in reference blood sample withdrawal} * \text{Rat weight (kg)}}$$

$$\text{RBF (mL/min)} = \frac{\text{Organ count} * \text{blood withdrawal flow (mL/min)}}{\text{Counts in reference blood sample withdrawal}}$$

$$\text{RBF (mL/min/g)} = \frac{\text{Organ blood flow (mL/min)}}{\text{Organ weight (g)}}$$

Statistical Analysis

The effects of drugs or saline on CO and RBF in different organs were evaluated by comparing drug or saline treatment with the baseline, utilizing a two-tailed Student's *t*-test for paired data. The baseline values for CO and RBF after different treatments were compared by using one way analysis of variance (ANOVA). Comparisons of changes in CO and RBF after AC or MET administration to those observed following saline were made by using a one way ANOVA. In all tests, a probability level of significance pre-set at $\alpha = 0.05$ was used. Results are expressed as mean ± S.E.M.

Results

The results in this study have been divided into three stages: Stage 1 results observed 1 min after administration of drugs or saline; Stage 2 results observed 10 min after administration of drugs or saline; Stage 3 results observed after chronic administration of drugs or saline.

The values of CO and RBF after saline administration did not differ significantly from the baseline values in this group (Table 1). There were no significant differences in baseline values either within drug treatment groups or the saline treatment group. The effects of AC and MET on CO and RBF in all stages are summarized in Tables 2 and 3. Both drugs reduced the CO significantly in both Stages 1 and 2 when compared with the baseline values. The percentage change in CO after administration of either drug however, was significantly different only in stage one when compared with the same values in saline group (Figures 1 and 2).

Changes in RBF occurred in parallel with the changes in CO (Tables 2 and 3). These values were reduced significantly in most organs when the blood flow was compared after drug administration with the baseline (Tables 2 and 3) in Stages 1 and 2. In Stage 1, the percentage changes in RBF after either AC or MET administration were significantly greater than in the saline group for the liver, heart and spleen (Figures 1 and 2)

Following multiple dose administration of either AC or MET, there were no significant differences between CO or RBF in any organs when compared with that of saline group (Figures 3 and 4).

Table 1. The acute effect of iv administration and the chronic effect of oral administration of saline, as control, on CO and RBF in Sprague–Dawley rats (six rats in each group). Data are presented as mean ± S.E.M.

Organs	Baseline	1 min	Baseline	10 min	Chronic
Liver	0.15 ± 0.03	0.13 ± 0.03	0.15 ± 0.02	0.12 ± 0.02	0.18 ± 0.01
Heart	3.92 ± 0.74	2.88 ± 0.46	2.74 ± 0.28	2.14 ± 0.55	2.44 ± 0.14
R-Kidney	3.84 ± 0.41	3.02 ± 0.35	4.05 ± 0.21	2.73 ± 0.20	2.91 ± 0.26
L-Kidney	3.85 ± 0.40	3.25 ± 0.39	3.79 ± 0.35	2.60 ± 0.28	3.06 ± 0.36
Spleen	1.80 ± 0.29	1.41 ± 0.19	1.53 ± 0.20	1.03 ± 0.15	1.04 ± 0.17
Stomach	0.46 ± 0.04	0.35 ± 0.04	0.47 ± 0.04	0.28 ± 0.04	0.39 ± 0.11
CO (mL/min/kg)	338 ± 27	304 ± 30	276 ± 15	228 ± 23	229 ± 22

Table 2. The acute effect of iv administration and the chronic effect of oral administration of AC on CO and RBF in Sprague–Dawley rats (six rats in each group). Data are presented as mean ± S.E.M.

Organs	Baseline	1 min	Baseline	10 min	Chronic
Liver	0.15 ± 0.02	0.08 ± 0.01[a]	0.14 ± 0.02	0.12 ± 0.02[a]	0.19 ± 0.01
Heart	4.14 ± 0.82	2.06 ± 0.36[a]	3.32 ± 0.46	2.29 ± 0.34	2.77 ± 0.42
R-Kidney	4.36 ± 0.52	2.54 ± 0.27[a]	3.60 ± 0.41	3.12 ± 0.55[a]	2.82 ± 0.26
L-Kidney	4.45 ± 0.62	2.73 ± 0.36[a]	3.6 ± 0.45	2.99 ± 0.56[a]	2.65 ± 0.25
Spleen	1.9 ± 0.36	0.69 ± 0.07[a]	1.47 ± 0.13	1.15 ± 0.27[a]	0.78 ± 0.08
Stomach	0.45 ± 0.07	0.37 ± 0.06	0.43 ± 0.11	0.39 ± 0.10	0.33 ± 0.07
CO (mL/min/kg)	437 ± 49	203 ± 32[a]	373 ± 52	283 ± 32	260 ± 20

[a] Significantly different from the baseline, $p < 0.05$.

Table 3. The acute effect of iv and the chronic effect of oral administration of MET on CO and RBF in Sprague–Dawley rats (six rats in each group). Data are presented as mean ± S.E.M.

Organs	Baseline	1 min	Baseline	10 min	Chronic
Liver	0.16 ± 0.03	0.10 ± 0.02[a]	0.17 ± 0.03	0.14 ± 0.03[a]	0.23 ± 0.03
Heart	4.00 ± 0.84	2.58 ± 0.54	3.39 ± 0.81	2.07 ± 0.48[a]	1.50 ± 0.25
R-Kidney	4.11 ± 0.47	2.66 ± 0.37[a]	3.91 ± 0.69	2.83 ± 0.41[a]	3.43 ± 0.32
L-Kidney	3.83 ± 0.42	2.39 ± 0.29[a]	3.82 ± 0.68	2.88 ± 0.37[a]	3.20 ± 0.32
Spleen	1.45 ± 0.23	0.84 ± 0.14[a]	1.26 ± 0.30	0.68 ± 0.15[a]	1.04 ± 0.21
Stomach	0.50 ± 0.07	0.29 ± 0.05[a]	0.37 ± 0.04	0.25 ± 0.05[a]	0.28 ± 0.03
CO (mL/min/kg)	378 ± 91	148 ± 48[a]	395 ± 97	233 ± 31	233 ± 12

[a] Significantly different from the baseline, $p < 0.05$.

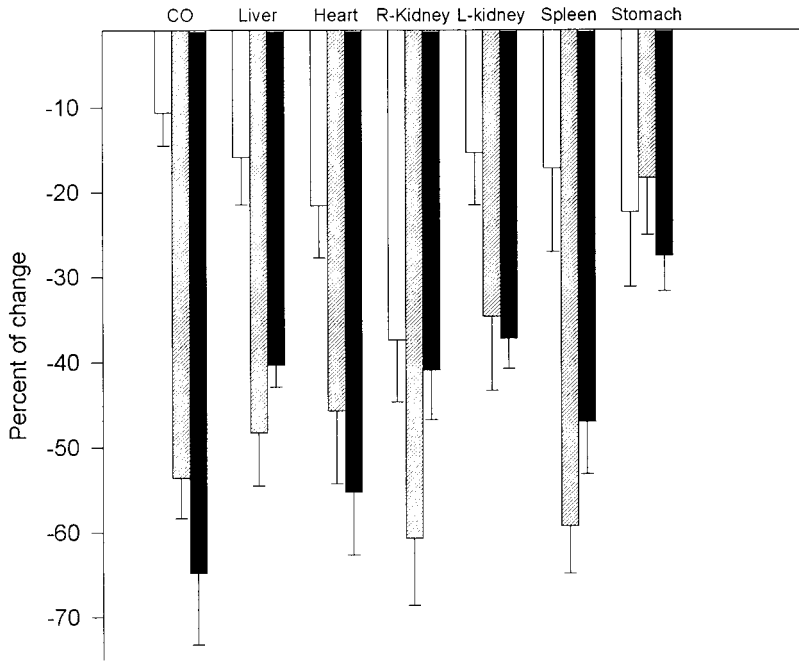

Figure 1. Percent of change in CO and RBF 1 min after administration of saline (open bars), AC (hatched bars) or MET (solid bars) in Sprague–Dawley rats (six rats in each group). Mean ± S.E.M.

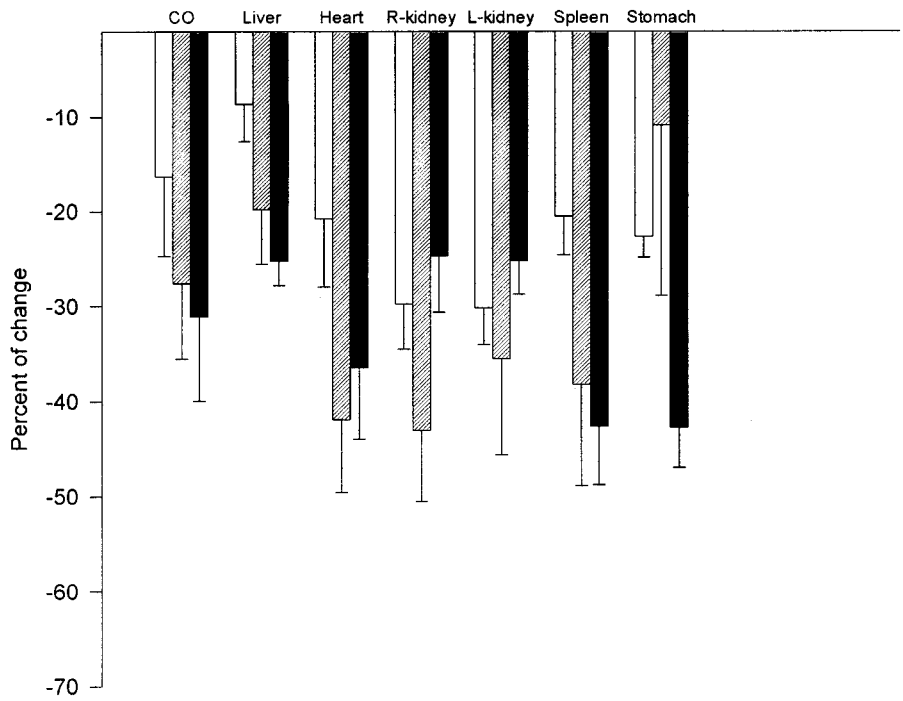

Figure 2. Percent of change in CO and RBF 10 min after administration of saline (open bars), AC (hatched bars) or MET (solid bars) in Sprague–Dawley rats (six rats in each group). Mean ± S.E.M.

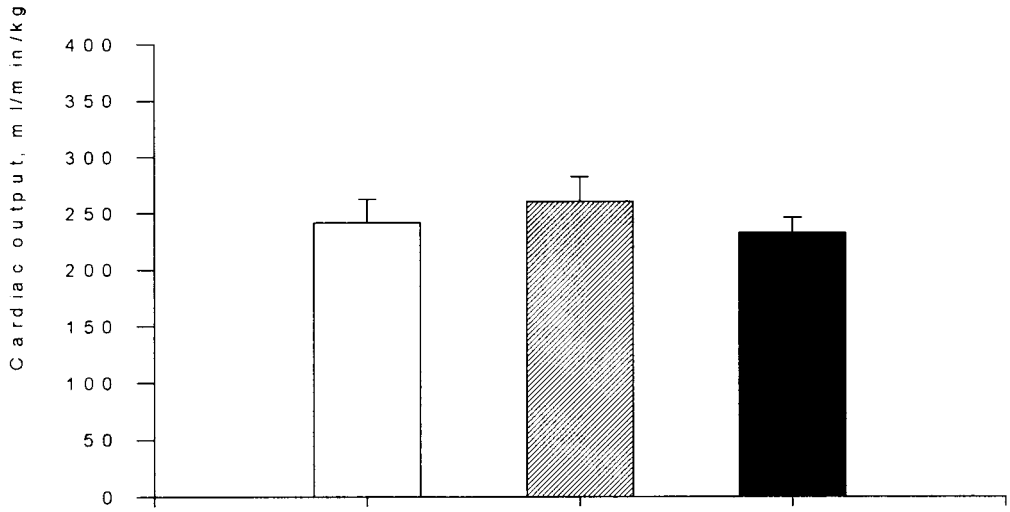

Figure 3. CO after 4 days treatment with saline (open bars), AC (hatched bars) and MET (solid bars) in Sprague–Dawley rats (six rats in each group). Mean ± S.E.M.

Discussion

The use of microspheres to measure simultaneously total CO as well as RBF has been validated and used in different animals [9–15] including rat [16–18]. In this study, the microsphere method was used to evaluate the effects of two different β-blockers with different ancillary properties on CO and RBF.

The precision of the microsphere technique depends on the number of microspheres trapped in the respective sample. It has been reported

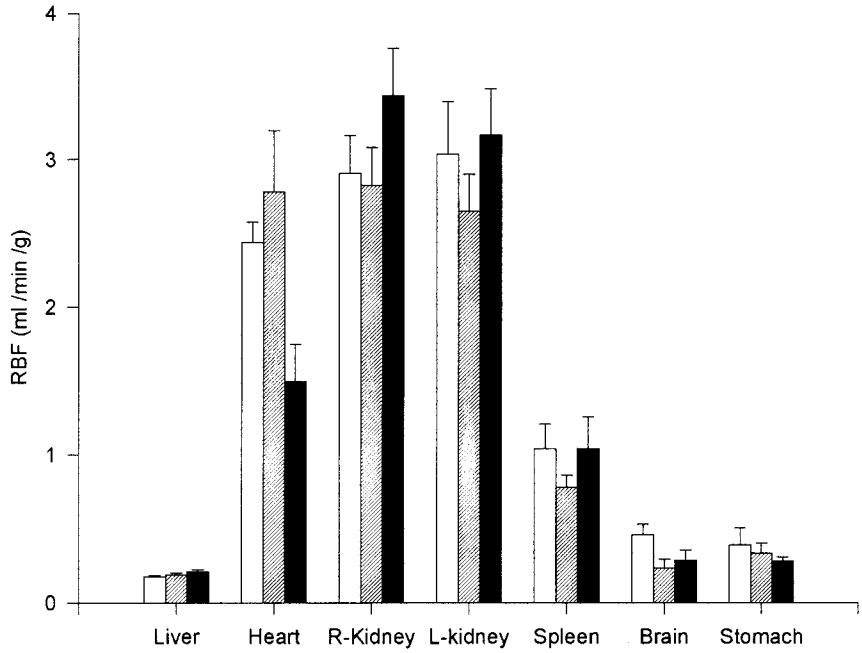

Figure 4. RBF after 4 days treatment with saline (open bars), AC (hatched bars) and MET (solid bars) in Sprague–Dawley rats (six rats in each group). Mean $\pm$ S.E.M.

that injection of 360000 microspheres or fewer will not cause any haemodynamic disturbances [19]. Furthermore, to have a reliable result, the number of microspheres should exceed 200 microspheres per sample to provide a precision of 10% at a confidence level of 95% for rat [20]. Thus, the number of microspheres was fixed approximately at 100000 microspheres so that each sample had more than 200 microspheres. Relatively few microspheres escaped trapping and passed through A-V shunts as judged by the total radioactivity contained in the lungs which was less than 3% of the amount injected. Small pieces of muscle and skin were also sampled in this study, but the number of microspheres in each of these samples was less than 200. Consequently, these samples were excluded from experiment and subsequent analysis. All other samples contained at least 400 microspheres as determined by specific activity of the microspheres and the radioactivity of each sample. Even distribution of microspheres to tissue was confirmed by the observation that approximately the same values for blood flow were observed in each kidney before and after drug administration.

Our results compare favourably to the CO and RBF reported by others in rat [21,22]. The CO of pentobarbital anaesthetized rat is variably quoted as being from 121 to 388 mL/min/kg. Harashima *et al*. [22] have reported data, using the microsphere method, which gave an average output of 331 ± 34 mL/min/kg, a value essentially the same as that obtained in the present study for baseline values (Tables 1–3).

The change in CO by two β-adrenoceptor blocking agents after the initial iv doses largely agree with previously reported response to these drugs when administered intravenously [23]. A rapid fall in CO was observed after acute administration of either AC or MET. As AC has a relatively low degree of ISA in comparison to other β-blockers, it may not have enough sympathomimetic activity to result in there being a significant difference in CO between this drug and MET, which has no ISA. Nonetheless, other investigators have also failed to detect any significant differences in haemodynamic changes caused by β-blockers with relatively low degree of ISA when they have compared them with the β-blockers which are devoid of ISA [23]. Moreover, Manttari *et al*. have also reported that the

haemodynamic differences between MET and AC are not statistically significant in hypertensive patients [25].

The change in RBF after acute administration of either AC or MET is striking. In nearly every tissue examined, there was a significant decrease in blood flow after either AC or MET administration when the blood flow was compared with the baseline values (Tables 2 and 3). When the percent of change in RBF is compared with the same value in a saline group however, it is significant only in the liver, heart and spleen 1 min after drug administration.

The haemodynamic effects of AC after chronic administration have also been reported by others [26,27]. In those studies, the hypotensive action of the drug in the long term was accompanied by a decrease in heart rate. The vascular resistance and CO however, returned to normal [28]. The finding that CO remains unchanged after long-term administration of AC is confirmed by the present study. However, the long-term antihypertensive response to β-blockers lacking partial agonist activity has also been reported to be invariably associated with a reduction on CO [24]. Our data is at contrast with these reports. The reduction in CO after administration of AC and MET was associated with a return of the initially reduced CO to normal values as we did not observe any significant differences between saline, MET and AC after chronic administration (Figure 3). The fact that CO, following long term administration of these two agents, is restored after an initial reduction of cardiac function implies that this is probably independent of the effect of ISA possessed by AC. Nevertheless, this is in agreement with other reports, which found the restoration of CO occurs after the administration of timolol and atenolol, two β-blockers devoid of ISA [29,30]. Furthermore, the restoration of CO after long-term administration has also been confirmed by comparing the long-term administration of atenolol and propranolol, β-blockers devoid of ISA, with AC, a β-blocker that possesses ISA [31].

In parallel with the CO, the RBF is not affected by chronic administration of either AC or MET. No significant differences in the liver, kidneys, heart, spleen or stomach blood flow were observed after chronic administration of either drug when compared with the saline values. Other investigators have also failed to detect any significant differences in organ blood flow after chronic administration of AC when they measured values in the calf muscle, and kidneys [28,31–33]. Similar results have also been reported for calf muscle and skin after long term administration of MET [34,35].

In conclusion, the present study demonstrates that AC and MET significantly reduced the CO and RBF in most organs after acute administration in rat when compared with the baseline values. However, these values returned to normal after chronic administration of either AC or MET. Thus, these results suggest that the additional property of ISA possessed by AC does not result in any statistically significant haemodynamic differences from MET. This may reflect an insufficient degree of ISA possessed by AC. The considerable inter-individual variability in this study may also explain the difficulty to detect any significant differences between these two agents.

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