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Effects of dronedarone and amiodarone on plasma thyroid hormones and on the basal and postischemic performance of the isolated rat heart

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Abstract

The present study investigated the effects of dronedarone and amiodarone on plasma thyroid hormones and the possible consequences on the response of the heart to ischemia. Amiodarone (30 mg/kg/day per os) or dronedarone (30 mg/kg/day per os) were administered for 2 weeks in normal and thyroxine-treated animals (25 μg/100 g body weight od sc, for 2 weeks), while animals without amiodarone and dronedarone served as controls. Isolated rat hearts were perfused in a Langendorff mode and subjected to 20 and 30 min of zero-flow global ischemia followed by 45 min of reperfusion. Functional changes were assessed by measuring left ventricular developed pressure (LVDP) under resting conditions and in response to ischemia–reperfusion, LVDP%, as well as the severity of ischemic contracture. Amiodarone resulted in increased T4, T4/T3 and rT3, whereas dronedarone did not alter the thyroid hormone profile in normal animals. In thyroxine-treated animals, amiodarone increased T4/T3 ratio but T4, T3 and rT3 levels were not altered. Basal functional parameters and ischemic contracture did not change by amiodarone and/or dronedarone neither in normal nor in thyroxine-treated hearts. In normal hearts, postischemic functional recovery, LVDP%, was not altered by amiodarone or dronedarone administration. LVDP% was statistically higher in thyroxine-treated hearts than in normal and this beneficial effect was not abolished by amiodarone or dronedarone treatment.

Keywords: Amiodarone; Dronedarone; Thyroid hormone; Ischemia; Heart, isolated, rat

1. Introduction

Antiarrhythmic drugs have been widely used in the treatment of patients with heart disease in order to reduce the incidence of sudden death. However, most antiarrhythmic compounds exert varying degrees of depressant action on the haemodynamics, which limit their use, particularly in patients with compromised left ventricular function. In addition, increased mortality has been reported with the use of some antiarrhythmic agents in patients with acute coronary syndromes (The Cardiac Arrhythmia Suppression Trial [CAST] Investigators, 1989). Amiodarone is a widely used antiarrhythmic agent that has been shown to be effective in reducing mortality in patients with heart failure and in survivors of myocardial infarction (Massie et al., 1996). Its beneficial effect has been suggested to be mediated through various mechanisms (Loh, 2000). However, amiodarone administration is often accompanied by side effects that might limit its use in certain circumstances. Particularly, amiodarone has been shown to exert a hypothyroid-like effect (Freedberg et al., 1970) with a decrease in plasma triiodothyronine (Venkatesh et al., 1986) and by the antagonism of thyroid hormone at the receptor level (Shahrara and Drvota, 1999; Drvota et al., 1995) and this effect could potentially modify the response of the heart to ischemia. In fact, recent clinical and experimental evidence show that thyroid hormone can be cardioprotective against ischemic injury, and thyroid hormone disorders might not be a desirable condition in the setting of the ischemic heart

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disease and heart failure (Pantos et al., 2001; Klein and Ojamaa, 2001). Though the role of amiodarone on the beneficial effect of thyroxine on the myocardium under resting conditions and in response to ischemia remains largely unknown. Dronedarone is a new non-iodinated derivative of amiodarone, with comparable electrophysiological effects (Sun et al., 1999) with possibly less side effects than amiodarone. However, this drug possesses antiadrenergic properties (Chatelain et al., 1995) that could potentially alter the basal myocardial performance while its effects on the response of the heart to ischemia has not been adequately studied.

Our study was designed to investigate whether amiodarone and dronedarone can alter thyroid hormone plasma levels and subsequently the response of the isolated rat heart to ischemia and whether coadministration of thyroxine with those antiarrhythmics can modify the inotropic and cardioprotective effect of thyroxine.

2. Methods

2.1. Animals

Seventy-two Wistar male rats, 330–380 g, were used for this study. The rats were handled in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985). Anaesthesia was achieved with intraperitoneal injection of ketamine hydrochloric acid (150 mg/kg).

2.2. Thyroxine administration

Hyperthyroidism was induced in rats by thyroxine administration. L-Thyroxine (T4) (Sigma, St. Louis, MO, USA) was dissolved in 99% ethanol by adding a small volume (20 μl) of 25% NaOH and diluted 33 times by adding 0.9% NaCl to obtain a stock solution of 1 mg ml^{-1}. Before each injection, a fresh solution was made in 0.9% NaCl to obtain a concentration of 50 μg T4 ml^{-1}. Thyroxine, 25 μg 100 g^{-1} body weight was given subcutaneously once daily for 14 days. This treatment results in a long-term moderate hyperthyroidism (Pantos et al., 1999, 2000, 2001). Normal rats were treated with subcutaneous injections of normal saline given once daily for 14 days.

2.3. Amiodarone and dronedarone administration

Amiodarone (30 mg/kg) or dronedarone (30 mg/kg) (Sanofi-Synthelabo, France) were given for 2 weeks once daily in normal and hyperthyroid animals per os. Before each administration, a fresh solution was prepared in 0.6% methylcellulose to obtain a concentration of 3 mg/ml. This dose regimen is closely related to the dose that is used in clinical practice.

2.4. Isolated heart preparation

A non-ejecting isolated rat heart preparation was perfused according to the Langendorff technique. In this model, coronary flow was adjusted so that the perfusion pressure at baseline to be similar for all the experimental groups (approximately 76 mm Hg). This resulted in a similar coronary flow per gram of tissue in all groups. The coronary flow thereafter was kept constant throughout the experiment. An intraventricular balloon allowed measurement of contractility under isovolumic conditions. Left ventricular balloon volume was adjusted to produce an average initial left ventricular end-diastolic pressure of 6 mm Hg in all groups and was held constant thereafter throughout the experiment. Since the balloon was not compressible, left ventricular contraction was isovolumic. As intraventricular volume was maintained at a constant value, diastolic fiber length, which represented preload, did not change. Thus, the left ventricular peak systolic pressure and the left ventricular developed pressure (LVDP), defined as the difference between left ventricular peak systolic pressure and left ventricular end-diastolic pressure, represented a contractility index obtained under isometric conditions. In this model of isolated rat heart preparation, an increase in minimal ventricular pressure is observed during ischemia, known as ischemic contracture.

Rats were anaesthetized with ketamine hydrochloric acid and heparin 1000 IU/kg was given intravenously before thoracotomy. The hearts were rapidly excised, placed in ice-cold Krebs–Henseleit buffer (composition in mmol/l: sodium chloride 118, potassium chloride 4.7, potassium phosphate monobasic, 1.2, magnesium sulfate 1.2, calcium chloride 1.4, sodium bicarbonate 25, and glucose 11) and mounted on the aortic cannula of the Langendorff perfusion system. Perfusion with oxygenated (95% O_2/5% CO_2) Krebs–Henseleit buffer was established within 60 s after thoracotomy. The perfusion apparatus was heated to ensure a temperature of 37 °C throughout the experiments. Hearts were paced at 320 bpm with a Harvard pacemaker. The pacemaker was turned off during ischemia. The water-filled balloon, connected to a pressure transducer and coupled to a Gould RS 3400 recorder was advanced into the left ventricle through an incision in the left atrium (Pantos et al., 1999, 2000, 2001).

2.5. Experimental protocol

Isolated normal and hyperthyroid rat hearts from animals treated with amiodarone or dronedarone and untreated animals, after an initial period of stabilization were subjected to 20 min of zero-flow global ischemia followed by 45 min of reperfusion.

Thus, the following experimental groups: normal rat hearts treated with saline (NORM, $n=13$), hearts from amiodarone-treated animals (NORM + A, $n=5$) and hearts from dronedarone-treated animals (NORM + D, $n=7$). In

addition, hearts from thyroxine-treated animals (THYR, $n=13$) served as controls to hearts from rats treated with amiodarone and thyroxine (THYR + A, $n=6$) or dronedarone and thyroxine (THYR + D, $n=7$).

Since ischemic contracture in normal hearts did not reach a peak at 20 min, in order to study the ischemic contracture in these animals, the period of ischemia was extended to 30 min. Thus, there were three additional groups: hearts from normal rats treated with saline [NORM (30), $n=8$], with amiodarone [NORM + A (30), $n=6$], and with dronedarone [NORM + D (30), $n=7$], respectively.

2.6. Measurement of thyroid hormone levels in plasma

Plasma T4, T3 and rT3 quantitative measurements were performed by using ^{125}I RIA (Radioimmunoassay) kits obtained from DiaSorin, Stillwater, MN, USA for T4 and T3 and from Biochem Immunosystems, Germany for rT3 (CA 1535M for T4, CA 1541 for T3 and 10834 for rT3). T4, T3 and rT3 levels were expressed as nanograms per milliliter of plasma.

2.7. Measurement of cardiac hypertrophy

Cardiac hypertrophy was assessed by the ratio of heart weight (HW) in milligrams to animal body weight (BW) in grams (HW/BW in mg/g) (Pantos et al., 1999, 2000).

2.8. Measurement of mechanical function

Left ventricular systolic function was assessed by recording the left ventricular developed pressure (LVDP, mm Hg), which was measured at the end of the stabilization period and after 45 min of reperfusion. LVDP and + dp/dt (mm Hg/s), − dp/dt (mm Hg/s) were used to assess baseline myocardial function. Postischemic myocardial function was assessed by recovery of LVDP and expressed as the percentage of the baseline value (LVDP%). Diastolic function was assessed by monitoring isovolumic left ventricular end-diastolic pressure (LVEDP, mm Hg) as a measure of diastolic chamber distensibility.

2.9. Measurement of temporal characteristics and severity of ischemic contracture

The time to peak contracture, T_{max} in minutes and the magnitude of peak contracture (increase in minimal value of left ventricular pressure during ischemia), C_{max} in millimeters of mercury, were recorded. (Pantos et al., 1999, in press).

2.10. Statistics

Values are presented as mean ± S.E.M. Unpaired *t*-test was used to test for differences between groups. One-way analysis of variance (ANOVA) followed by Bonferroni test was used when multiple comparisons were carried out. A two-tailed test with a P value less than 0.05 was considered significant.

3. Results

3.1. Thyroid hormone levels in plasma

T4, T3 and rT3 were higher in thyroxine-treated animals as compared to normal animals, $P<0.05$ (Table 1). Amiodarone resulted in significantly higher T4, T4/T3 and rT3 levels in normal animals as compared to non-treated normal animals, $P<0.05$. Dronedarone did not exert such an effect on thyroid hormone levels in normal animals. In thyroxine-treated animals, amiodarone increased T4 plasma concentration but not at a statistically significant level. This resulted in a significantly higher T4/T3 ratio as compared to non-treated hyperthyroid animals. T3 and rT3 levels were not altered. Dronedarone did not change the thyroid hormone profile in the hearts from thyroxine-treated rats (Table 1).

3.2. Cardiac hypertrophy

Thyroxine administration resulted in the development of cardiac hypertrophy. HW/BW ratio was higher in THYR than in NORM 3.9 ± 0.1 vs. 3.4 ± 0.1, $P<0.05$.

Amiodarone or dronedarone administration did not result in reduction of thyroxine induced cardiac hypertrophy at a statistically significant level: HW/BW ratio was 3.9 ± 0.1 for THYR + A and 4.1 ± 0.2 for THYR + D not significantly different from the non-treated hyperthyroid hearts (THYR); 3.9 ± 0.1, $P>0.05$.

HW/BW ratio was 3.3 ± 0.08 for NORM + A and 3.3 ± 0.1 for NORM + D not significantly different from the non-treated normal hearts (NORM); 3.4 ± 0.1, $P>0.05$.

3.3. Cardiac function under resting conditions

In THYR hearts, a significant increase in contractility and relaxation was observed without changes in the left ventricular developed pressure as compared to NORM hearts (Table 2). Amiodarone or dronedarone administration

Table 1
Thyroid hormone levels in plasma (ng/ml) in normal and hyperthyroid rats with and without amiodarone (A) or dronedarone (D) administration

Group	T4	T3	T4/T3	rT3
NORM	45.6 ± 3.3	0.8 ± 0.04	56 ± 4	84 ± 10
NORM + A	66.5 ± 1.4[a]	0.7 ± 0.03	86 ± 5[a]	180 ± 14[a]
NORM + D	33.7 ± 2.5	0.7 ± 0.08	46 ± 4	60 ± 7
THYR	667 ± 60[a]	6.8 ± 0.5[a]	97 ± 5[a]	1725 ± 113[a]
THYR + A	829 ± 70	6.4 ± 0.3	132 ± 11[b]	1888 ± 112
THYR + D	670 ± 86	6.7 ± 0.6	105 ± 16	1425 ± 85

[a] $P<0.01$ vs. NORM.
[b] $P<0.01$ vs. THYR.

Table 2
Functional baseline characteristics in all experimental groups with and without administration of amiodarone (A) or dronedarone (D)

Group	*n*	LVDP	+dp/dt	−dp/dt
NORM	13	108.6 ± 3.3	3407 ± 157.9	2384 ± 79.1
NORM + A	5	110.8 ± 2.4	3420 ± 111.3	2460 ± 67.8
NORM + D	7	110.0 ± 1.7	3385 ± 55.3	2400 ± 53.5
THYR	13	115.0 ± 3.5	4092 ± 168.8[a]	2723 ± 111.6[a]
THYR + A	6	115.3 ± 12.5	3816 ± 213.5	2700 ± 146.0
THYR + D	7	109.7 ± 4.0	3614 ± 181.8	2514 ± 110

LVDP = left ventricular developed pressure during stabilization period in mm Hg. +dp/dt = positive increase rate of left ventricular pressure in mm Hg/s. −dp/dt = negative increase rate of left ventricular pressure in mm Hg/s.
[a] $P < 0.05$ vs. NORM.

in normal and hyperthyroid animals did not alter the baseline functional characteristics of those hearts as compared to the hearts from non-treated animals (Table 2).

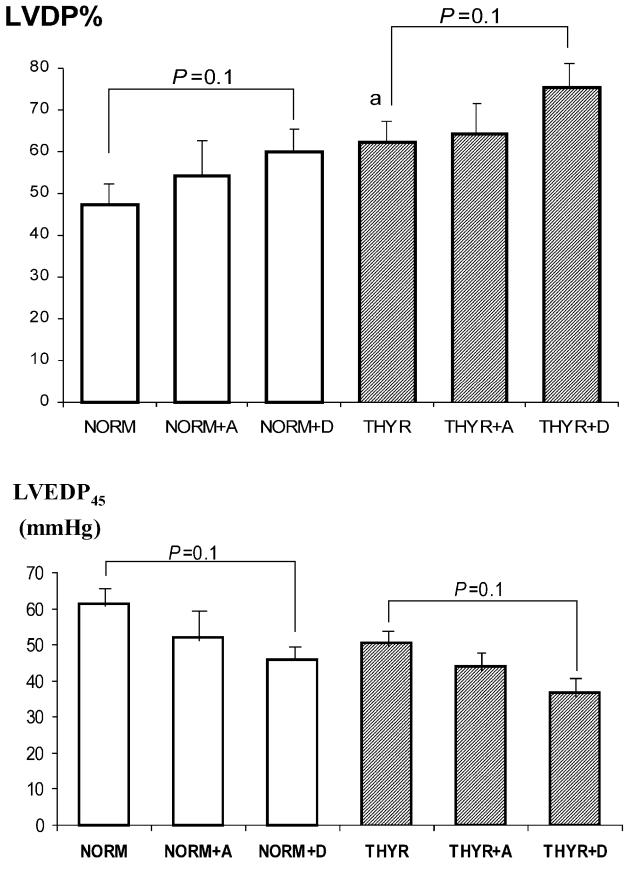

Fig. 1. Postischemic recovery of function, LVDP%, (upper panel) and left ventricular end-diastolic pressure at 45 min of reperfusion, $LVEDP_{45}$, (bottom panel) in normal hearts and hearts from hyperthyroid rats with and without amiodarone (A) or dronedarone (D) administration subjected to 20 min of ischemia. Dronedarone had a trend towards a higher LVDP% ($P = 0.1$) in both normal and thyroxine-treated hearts. LVDP% was higher in THYR than in NORM hearts ($P < 0.05$) and was not altered by amiodarone administration ($P > 0.05$). Dronedarone had a trend towards a lower $LVEDP_{45}$ ($P = 0.1$) in both normal and thyroxine-treated hearts. $LVEDP_{45}$ was not different in THYR as compared to NORM hearts ($P > 0.05$) and was not altered by amiodarone administration ($P > 0.05$). (ANOVA followed by Bonferroni test), [a]$P < 0.05$ vs. NORM.

3.4. Postischemic cardiac function

3.4.1. Twenty minutes of ischemia

LVDP% was not statistically different between amiodarone-treated hearts and non-treated hearts. However, with dronedarone administration, a trend towards an increased postischemic recovery was observed, though without reaching statistically significant levels, in both normal and thyroxine-treated hearts (Fig. 1, upper panel). In addition, LVEDP at 45 min of reperfusion ($LVEDP_{45}$) was not statistically different between amiodarone-treated hearts and non-treated hearts (Fig. 1). However, with dronedarone administration, a trend towards a reduced $LVEDP_{45}$ was observed, though without reaching statistically significant levels, in both normal and thyroxine-treated hearts (Fig. 1, bottom panel).

In thyroxine-treated hearts, LVDP% was statistically higher than in normal hearts, while $LVEDP_{45}$ was not statistically different (Fig. 1).

3.4.2. Thirty minutes of ischemia

LVDP% was 24.1 ± 2.7 for NORM (30) vs. 18.9 ± 5.5 for NORM + A (30), $P > 0.05$ and vs. 21.5 ± 4.3 for NORM + D (30), $P > 0.05$. LVEDP at 45 min was 86.0 ± 4.6 for NORM (30) vs. 84.0 ± 10.6 for NORM + A (30), $P > 0.05$ and vs. 82.8 ± 6.1 for NORM + D (30), $P > 0.05$.

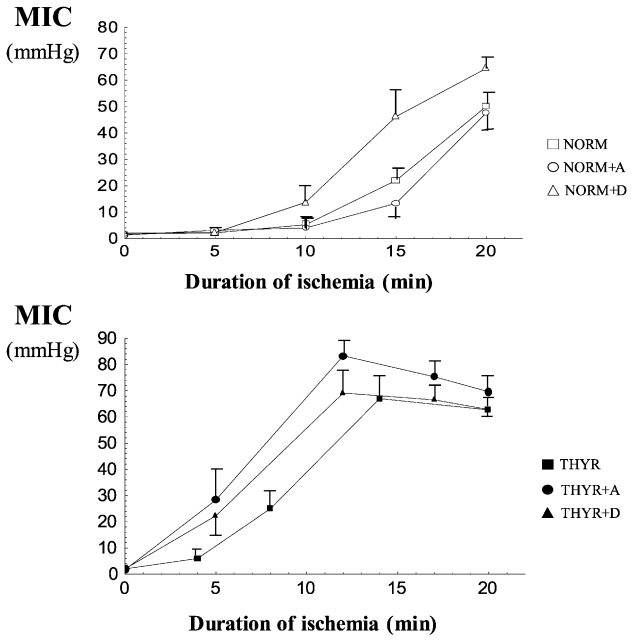

Fig. 2. Ischemic contracture profiles of normal (upper panel) hearts and hearts from hyperthyroid rats (bottom panel) with and without amiodarone (A) or dronedarone (D) administration subjected to 20 min of ischemia. MIC = the variation with time of magnitude of ischemic contracture. Ischemic contracture was accelerated in thyroxine-treated hearts, while normal hearts did not reach a peak within 20 min of ischemia. Amiodarone or dronedarone administration did not alter the ischemic contracture profile either in normal or in thyroxine-treated hearts.

3.4.3. Ischemic contracture

In normal hearts, contracture did not reach a peak within 20 min of ischemia (Fig. 2). In hyperthyroid hearts, contracture occurred earlier and within the 20 min of ischemia, while amiodarone or dronedarone administration did not alter the mode of contracture (Fig 2).

In order to study the effects of amiodarone and dronedarone on normal hearts, we extended the period of ischemia to 30 min. T_{max} was found to be 21.9 ± 0.8 for NORM (30) animals vs. 20.5 ± 1.3 for NORM + A (30), $P > 0.05$ and vs. 24.0 ± 1.5 for NORM + D (30), $P > 0.05$. C_{max} was 63.2 ± 3.2 for NORM (30) animals vs. 63.6 ± 12.7 for NORM + A (30), $P > 0.05$ and vs. 55.1 ± 1.9 for NORM + D (30), $P > 0.05$.

4. Discussion

The present study has investigated the effects of long-term amiodarone and dronedarone administration on thyroid hormone metabolism and the subsequent effects on the response of the heart to ischemia and reperfusion.

Our data showed that amiodarone administration in normal animals resulted in increased T4, rT3 and T4/T3 while T3 was not changed. Similar data are reported by previous studies. In fact, in a rat model, it was found that after 4 weeks of 5, 15, 45 mg/kg body weight amiodarone administration in rats, serum T4 was increased, whereas T3 did not change (Sogol et al., 1983). Furthermore, in mice, amiodarone administration of 50 mg/kg for 2 weeks, it was shown to increase serum T4 while serum T3 was decreased (Shahrara and Drvota, 1999). These data suggest that, in rats treated with amiodarone, peripheral conversion of T4 to T3 is decreased, probably due to the reduced deiodination of T4 to T3, while a preferential production of rT3 occurs. In addition, this study showed that the defect of the peripheral conversion of T4 to T3 after amiodarone administration is not abolished by thyroxine treatment. In fact, T4/T3 was found to be increased in rats treated with thyroxine and amiodarone as compared to hearts treated only with thyroxine. T4, T3 and rT3 though were not statistically different between those groups.

Thyroid hormone disorders can play an important role in cardiac contractility and also in the response of the heart to ischemic stress (Klein and Ojamaa, 2001; Pantos et al., 2001). Thyroid hormones were found to be decreased in the acute phase of myocardial infarction and lower thyroid hormone levels corresponded to a greater extent of myocardial injury (Ojamaa et al., 2000; Kimura et al., 2000). Furthermore, thyroxine pretreatment was shown to increase the tolerance of the heart to ischemia and accelerate ischemic contracture in a similar pattern as ischemic preconditioning (Pantos et al., 2000, 2001, in press). Amiodarone's adverse effects on thyroid hormone could potentially deteriorate the functional state of the myocardium under resting conditions and in response to ischemic stress. Furthermore, the beneficial effect of thyroxine pretreatment on the myocardium under resting conditions and in response to ischemia might be abolished by concomitant administration of amiodarone and thyroxine.

In the present study, amiodarone administration was not found to have a negative inotropic effect or to deteriorate postischemic recovery of function in normal hearts. During ischemia, ischemic contracture was not shown to be altered. Coadministration of thyroxine and amiodarone did not abolish thyroxine-induced cardioprotection and ischemic contracture occurred earlier in thyroxine-treated than in normal hearts while it was not altered by amiodarone administration. Furthermore, amiodarone did not prevent the development of cardiac hypertrophy induced by thyroxine administration. These data might be explained by the fact that in our model, the levels of T3 were not altered. Amiodarone though, apart from its effect on thyroid metabolism has been found to down-regulate the $\alpha 1$ and $\beta 1$ receptor mRNA in mouse myocardium (Shahrara and Drvota, 1999) and competitively inhibit the binding of T3 to its nuclear receptor in a dose-dependent manner (Drvota et al., 1995). In this model though, as our data show, those effects of amiodarone do not seem to be of physiological significance. This is probably due to the dose and the time course of amiodarone administration used in this study.

However, it is reported that amiodarone can have a cardioprotective effect against ischemia. In fact, with higher doses of amiodarone (240 mg/kg instead of 30 mg/kg, od) and for longer periods of time (4 weeks), amiodarone was found to improve rather to deteriorate postischemic recovery of function after 15 min of global ischemia (Karlson et al., 1990). Furthermore, acute administration of amiodarone was shown to protect cardiac myocytes against oxidative injury by its free radical scavenging action (Ide et al., 1999). In the present study, we failed to observe similar results probably due to the differences in our experimental design.

Dronedarone, is a non-iodinated analogue that has been found to have comparable to amiodarone electrophysiological effects without the adverse effects of amiodarone (Sun et al., 1999). In fact, in the present study, dronedarone had no effect on thyroid hormones. However, its antiadrenergic properties (Chatelain et al., 1995) could potentially display a negative inotropic effect on the myocardium. Our study though showed that dronedarone administration did not result in depressed contractility under resting conditions. Furthermore, dronedarone administration improved rather than deteriorated the response of the heart to ischemia. In fact, in less severe ischemia such as 20 min of ischemia, a trend towards a significant increase in postischemic recovery of function was found. However, with a longer period of ischemia, this beneficial effect was not observed. This finding probably implies that dronedarone has only a weak anti-ischemic effect that might be attributed to dronedarone-induced nitric oxide-dependent coronary vasorelaxation (Guiraudou et al., 1998). Coadministration of thyroxine and dronedarone did not alter the thyroxine induced effect

on myocardium under resting conditions and in response to ischemia-reperfusion. Furthermore, dronedarone did not interfere with the development of cardiac hypertrophy induced by thyroxine administration.

It appears that amiodarone and dronedarone can be used in the setting of ischemia without modifying the tolerance of the heart to ischemia or impairing the myocardial performance. Furthermore, they can be concurrently administered with thyroxine, without interfering with its beneficial effects on the heart, whereas potentially preventing the induction of arrhythmias. These properties might be desirable for the use of these agents in clinical conditions where arrhythmias are associated with impaired left ventricular function.

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