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Treatment of ischaemic left ventricular dysfunction with milrinone or dobutamine administered during coronary artery stenosis in the presence of beta blockade in pigs†

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Background. This study examines the effects of phosphodiesterase type III (PDEIII) inhibition *vs* beta stimulation on global function of the left ventricle (LV) and systemic haemodynamics in a porcine model of acute coronary stenosis with beta blockade.

Methods. A total of 18 adult swine were anaesthetized. Micromanometer-tipped catheters were placed in the ascending aorta and LV. Two pairs of ultrasonic dimension transducers were placed in the subendocardium on the short axis proximal to a left anterior descending (LAD) artery occluder and the long axis of the LV. Before ischaemia, i.v. esmolol was infused to decrease baseline heart rate (HR) by approximately 25%, and all animals received an esmolol infusion (150 $\mu g\ kg^{-1}\ min^{-1}$). Ischaemia was produced by reducing the flow in the LAD artery by approximately 80%, from 17(4) to 3(2) ml min^{-1}. Animals were randomized to receive (after esmolol) one of the following: no drug, sham only (Group 1, n=6), control (C); 50 $\mu g\ kg^{-1}$ i.v. milrinone (Group 2, n=6) followed by 0.375 $\mu g\ kg^{-1}\ min^{-1}$ (M); or incremental doses of dobutamine (Group 3, n=6) every 10 min (5, 10 and 20 $\mu g\ kg^{-1}\ min^{-1}$) (D). Left ventricular function data obtained included HR, arterial and LV pressures, cardiac output (CO), Emax and dP/dT. Measurements were taken during five time periods: before ischaemia (at baseline, after esmolol) and every 10 min during ischaemia (at 10, 20 and 30 min).

Results. The effects of beta blockade and ischaemia had a significant impact on contractility (Emax) in Group M and myocardial performance (left ventricular end-diastolic pressure, LVEDP) in all groups. Left ventricular function (Emax, CO, LVEDP and SVR) was better preserved when milrinone was added in Group M. A moderate dose of dobutamine (10 $\mu g\ kg^{-1}\ min^{-1}$) increased CO. Only the high dose (20 $\mu g\ kg^{-1}\ min^{-1}$) improved contractility (Emax), but at the expense of increased SVR. Also, LVEDP with either dose of dobutamine remained high and unchanged.

Conclusions. From our limited findings, it would appear that there may, theoretically, be some benefit for using milrinone in preference to other inotropic drugs in the presence of beta blockade. Milrinone administration should be considered in patients with acute ischaemic LV dysfunction and preexisting beta blockade before using other inotropic drugs such as beta stimulants.

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Transient coronary artery occlusion is associated with metabolic derangement that can result in prolonged myocardial dysfunction.[1] Milrinone has both inotropic and vasodilatory properties that have been demonstrated, like

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other phosphodiesterase (PDE) inhibitors, to improve myocardial function without increasing oxygen consumption.[2 3] This protective effect is probably based on its ability to improve left ventricular performance and increase blood flow to the ischaemic myocardium.[3]

Beta blockers are used to prevent and limit myocardial ischaemic damage and improve perioperative outcome.[4] With preexisting beta blockade, however, ischaemia-induced left ventricular dysfunction may worsen cardiac function and haemodynamics because of the additive effects on contractility. There is very little information that addresses the known protective effect of preoperative treatment with beta blockers in combination with pre-ischaemic[5] or post-ischaemic treatment of heart failure[6 7] with PDE inhibitors, except for a few suggestive non-ischaemic clinical[8–10] or laboratory[11] studies. The combination of PDE type III (PDEIII) inhibitor and beta blockade is still under investigation in a large, multicentre, double-blind, randomized trial.[7]

Beta-adrenergic agonists are commonly utilized to increase contractility. Their effects may be less predictable in the presence of acute beta blockade. PDEIII inhibitors do not require interaction with beta receptors, and they increase coronary flow and decrease wall stress; thus, their use may result in a more favourable haemodynamic profile, while preserving the benefits of beta blockade.[11 12] There are very few studies addressing the known protective effect of preoperative treatment with beta blockers in combination with the known protective effect of pre-ischaemic treatment with PDE inhibitors. It was demonstrated in non-ischaemic animal studies that beta blockade can attenuate the hypotensive and chronotropic effects, but not the positive inotropism or preload reduction induced by milrinone.[13] Another study showed that treatment of dogs with amrinone, another PDE inhibitor, reversed the untoward effects of potent cardiodepressant drugs, such as calcium and beta blockers, even in the presence of inhalation anaesthetics.[12] Treatment with milrinone in patients taking beta blockers improved haemodynamics and organ perfusion during off-pump coronary artery grafting when given prophylactically[14 15] or when haemodynamic deterioration took place.[16] The beneficial effect as a result of decreased demand is an essential factor that has been demonstrated in many studies evaluating the protective effect of drugs or manipulations that have a positive effect on myocardial metabolism.[4 5 17 19]

This study examines the effects of PDEIII inhibition *vs* beta stimulation on global left ventricular function and systemic haemodynamics in a porcine model of acute coronary stenosis with beta blockade. We hypothesized that this PDEIII inhibitor may be superior because of its ability to increase myocardial supply/demand ratio.

Methods

The protocol was approved by the University of Florida Institutional Animal Care and Use Committee. The use of animals was in accordance with the guidelines established by the animal research division. Animals were handled in accordance with guidelines established by the National Institutes of Health (NIH publication 85-23, revised 1985).

Eighteen domestic swine weighing 50–53 kg were premedicated with i.m. ketamine (35 mg kg^{-1}) and anaesthetized with isoflurane in 100% oxygen. A tracheostomy was then performed, and the animals' lungs were mechanically ventilated at 12 b.p.m., with tidal volumes of 12 ml kg^{-1} to maintain an end tidal CO_2 between 4.2 and 4.7 kPa. Anaesthesia and mechanical ventilation were maintained with the use of a Narkomed 4 anaesthesia machine (North American Dräger, Telford, PA, USA). Pancuronium was utilized for muscle relaxation during surgical preparation. A 7 French (Fr) pressure-tipped, flotation pulmonary artery catheter (Millar Instruments Inc., Houston, TX, USA) was inserted via the right internal jugular vein into the main pulmonary artery through an 8 Fr Cordis introducer (Arrow International, Reading, PA, USA). A 7 Fr, triple lumen, central venous catheter was placed through the left internal jugular vein. The left carotid artery was exposed, and a 5 Fr pressure-tipped catheter (Millar Instruments Inc.) was placed and advanced into the ascending aorta for continuous arterial pressure monitoring. A median sternotomy was then performed and the heart placed in a pericardial cradle.[4 18–20] A 5 Fr pressure-tipped catheter (Millar Instruments Inc.) was inserted via a small stab wound in the apex into the left ventricular cavity for measurement of left ventricular pressure.

The left anterior descending (LAD) coronary artery was isolated proximal to the first major branch diagonally and loosely encircled with a ligature.[3] A constrictor was placed in the LAD coronary artery between the first and second diagonal arteries. Ischaemia was produced by reducing the flow in the LAD artery by approximately 80%. This is comparable with previous and similar model studies of coronary stenosis, which created similar haemodynamic and metabolic changes in dogs[18–22] and pigs.[5] Flow meter probes were placed on the aortic root and the LAD artery for cardiac output (CO) and coronary flow measurements.

Two pairs of ultrasonic dimension tranducers were placed in the subendocardium on the short axis proximal to a LAD artery occluder and the long axis of the left ventricle. The inferior vena cava was encircled with an umbilical tape to produce acute reductions in preload.

Maintenance of intravascular volume was accomplished with lactated Ringer's solution administered by continuous infusion through a peripheral vein at a rate of 10 ml kg^{-1} h^{-1}. Normothermia (pulmonary artery temperature of 37°C) was maintained by the application of a warming blanket. All animals were allowed to stabilize for 1 h following surgical preparation prior to data collection.

Haemodynamic measurements

Haemodynamic measurements included systemic arterial pressure, pulmonary artery pressure, left ventricular

pressure, central venous pressure, CO, Emax and LV dP/dT as contractility parameters. Emax, in particular, is a relatively load-independent index of contractility, whereas dP/dT is known to be afterload-dependent. Electrocardiographic (standard lead II) findings and heart rate (HR) were recorded continuously and CO was measured by the aortic flow probe. Pulmonary and systemic vascular resistances were calculated using standard formulae (SVR=MAP−CVP/CO, where SVR=systemic vascular resistance; MAP=mean arterial pressure; CVP=central venous pressure; CO=cardiac output). All transducers were connected to a biomedical amplifier (Grass model 7D, Grass Instruments Co., Quincy, MA, USA). The signals were digitized and continuously recorded at 200 Hz on a personal computer for later analysis (Sonometrics Corp., London, Ontario, Canada).

Left ventricular volumes were derived automatically from changes in dimension determined from sonomicrometry in the long and short axes. The formula of an ellipsoid was assumed, utilizing commercially available software (Sonometrics Corp.).

I.V. esmolol was infused to decrease baseline HR by approximately 25% before the induction of ischaemia. All animals received an esmolol infusion (150 μg kg^{-1} min^{-1}) before induction of ischaemia. Ischaemia was produced by reducing the flow in the LAD artery by approximately 80%. Measurements were taken during five time periods: before ischaemia (at baseline, after esmolol) and every 10 min during ischaemia (at 10, 20 and 30 min). During each period of data collection, the inferior vena cava was constricted with the umbilical tape for approximately six to eight beats in order to construct a series of pressure–volume loops and determine the slope of the end-systolic pressure–volume relationship (Emax).

Use of Emax, the slope of the end-systolic pressure–volume relationship, as an index of contractility (and insensitive to loading conditions), was introduced by Suga in the early 1970s.[23 24] The time-dependent ratio of pressure to volume, $E(t)$, represents the elastance of the ventricle, and Emax, the maximal value of $E(t)$, is independent of preload and afterload and can be a reliable index of ventricular contractility. Using an intact circulation model Kass,[25] calculated Emax during the release of inferior vena cava occlusion and used the changes in venous return to detect changes in sympathetic activity or contractility. That particular model, which used vena cava occlusion, has been reported in multiple studies since the 1990s.[26] The vena cava ligature we used (umbilical tape with a rubber ligature) has been described in detail. Other alternatives are the introduction of a balloon-tipped urinary catheter via the femoral artery inflated for several seconds to produce an acute reduction in preload.[26]

Animal groups

All groups received an esmolol infusion (150 μg kg^{-1} min^{-1}). Animals were randomized to receive (after esmolol) one of the following: no drug, sham only (Group 1, n=6), control (C); 50 μg kg^{-1} i.v. milrinone (Group 2, n=6), followed by another 0.375 μg kg^{-1} min^{-1} (M); or incremental doses of dobutamine (Group 3, n=6) every 10 min (5, 10 and 20 μg kg^{-1} min^{-1}) (D).

Statistical analysis

Values were expressed as mean (SD). A two-way ANOVA was utilized, followed by Student Newman–Keuls test for multiple comparisons. A P<0.05 was considered significant.

Results

Baseline haemodynamic data were similar between groups (Table 1). Changes in CO followed the same trend in all groups (CO changes were significant, with a P-value<0.05) as HR changes when esmolol, applied before ischaemia, was used in the three groups treated (control, milrinone and dobutamine groups). CO (mean values) was reduced by 30% (P=0.014), 13%, (P=0.03) and 11% (P=0.03),

Table 1 Measured and calculated haemodynamic and contractility data (baseline, esmolol, ischaemia periods) with no drug (Group C), milrinone (Group M) or dobutamine (Group D). Data expressed as mean values (SD) of the mean. *P<0.05 compared with ischaemia (without drug) period, in the same group. †P<0.05 compared with baseline period, in the same group. HR, heart rate; SBP, systolic blood pressure; CO, cardiac output; SV, stroke volume; LVEDP, left ventricular end-diastolic pressure; LAD, left anterior descending; SVR, systemic vascular resistance

	Baseline			**Esmolol**			**Ischaemia without drug**		
	Control	**Milrinone**	**Dobutamine**	**Control**	**Milrinone**	**Dobutamine**	**Control**	**Milrinone**	**Dobutamine**
Haemodynamic variables									
HR (beats min^{-1})	104 (14)*	94 (17)*	97 (13)*	82 (11)†	75 (13)†	80 (10)†	83 (6)†	77 (14)†	82 (7)†
SBP (mm Hg)	88 (7)	83 (12)	79 (12)	90 (10)	82 (16)	78 (80)	82 (12)	80 (12)	86 (7)
CO (litre min^{-1})	2.6 (0.8)	2.3 (0.6)	2.7 (0.7)	1.8 (0.6)†	2 (0.5)	2.4 (0.6)	1.7 (0.5)†	1.7 (0.3)†	2.4 (0.7)
SV (ml $beat^{-1}$)	25.6 (7.7)	25.5 (7.5)	28.4 (8.7)	21.4 (6.7)	27.9 (10.7)	29.4 (8.7)	21.0 (4.6)	22.3 (4.7)	29.2 (9.8)
LVEDP (mm Hg)	4 (2)*	4 (3)*	5 (1)*	5 (2)*	7 (4)	5 (2)*	9 (3)†	11 (5)†	9 (3)†
LAD flow (ml min^{-1})	14 (3)*	17 (4)*	18 (2)*	11 (3)	15 (3)	16 (3)	3 (1)†	3 (2)†	5 (2)†
SVR (dyn s cm^{-5})	1405 (428)	1270 (367)	1085 (508)	1921 (725)	1400 (293)	1139 (401)	1762 (835)	1641 (167)	1196 (377)
Contractility variables									
dP/dT (mm Hg s^{-1})	64 (8)	57 (3)	56 (12)	64 (17)	55 (10)	51 (7)	57 (12)	61 (9)	55 (5)
Emax (mm Hg ml^{-1})	4.7 (0.5)	5.0 (0.5)	4.8 (0.3)	4.3 (0.6)	4.5 (0.3)*	4.6 (0.4)	3.8 (0.7)	3.9 (0.2)†	4.1 (0.5)

respectively. HR was reduced by 21, 20 and 18%, respectively (P=0.001 for control and dobutamine and P=0.003 for the milrinone group). There was no significant difference between the three groups regarding baseline and esmolol periods for all haemodynamic parameters. When stroke volume (SV) was calculated (taking into consideration simultaneous changes in CO and HR), there were no significant changes within the groups before induction of ischaemia, similar to the lack of significant changes within the groups for other measurements of left ventricular function, with dP/dT representing contractility.

There are no statistically significant differences between the three groups (control, milrinone and dobutamine) for all indicators of cardiac performance (CO, SV) or contractility (dP/dT, Emax) before (baseline and esmolol periods) and during ischaemia without drugs (without milrinone or dobutamine). Measurements of CO and SV were not significantly different between the three groups following ischaemia with and without drugs. Emax was reduced in all three groups (control, milrinone, dobutamine) to a similar degree (19, 22 and 15% for mean values, respectively). The reduction in the milrinone group (statistically significant within the group P=0.001 *vs* baseline value in the same group=milrinone group), was not significant between groups.

Coronary stenosis, or partial occlusion with significant flow reduction, created myocardial ischaemia. During beta blockade and ischaemia, LAD artery flow was reduced significantly from 17(4) to 3(2) ml min^{-1} (P=0.001). This combination had a significant impact on contractility (Emax) and left ventricular end-diastolic pressure (LVEDP). Beta blockade with ischaemia (without drugs) produced a depression in Emax, which was statistically significant (P=0.001) *only* in the milrinone group, concomitant with a significant increase in LVEDP in all groups (P=0.001 for all groups) (Table 1).

These changes persisted for 30 min over the ischaemic period in the control group (Table 2). During ischaemia and preexisting beta-blockade, left ventricular function was better preserved with additional milrinone in Group M: the Emax was preserved (P>0.05 non-significant from baseline) during ischaemia (with drugs) and returned to baseline values following a significant reduction during ischaemia without milrinone (P=0.001 *vs* baseline values) (Tables 1 and 2; Fig. 2); CO was higher (P=0.03 *vs* ischaemia without drug), and LVEDP and SVR were lower (P=0.001 *vs* ischaemia without drug) in Group M; the significant changes seen in Emax, CO, LVEDP and SVR did not appear in the control group (C) (Fig. 1, Table 2).

A moderate dose of dobutamine (10 μg kg^{-1} min^{-1}) increased CO (P=0.01) (Table 2). However, only the high dose (20 μg kg^{-1} min^{-1}) improved contractility (Emax), but at the expense of an increased SVR (Table 2, Fig. 2). Left ventricular end-diastolic pressure with either dose of dobutamine remained unchanged and high compared with baseline (Table 2).

Discussion

The question we attempted to answer in our study was: Would this PDEIII inhibitor, in the presence of beta blockade, be superior to a beta stimulant? We hypothesized that, in presence of 'non-interfered' (=no beta stimulant) beta blockade, a PDEIII inhibitor will decrease or reverse myocardial depression as a result of decreased demand, more so than beta stimulation in the presence of beta blockade.

The results of this study demonstrate that under general anaesthesia, during ischaemic cardiac dysfunction in the presence of beta blockade, the use of milrinone was associated with a favourable profile of ventricular function and systemic haemodynamics. In contrast, only the high dose of

Table 2 Measured and calculated haemodynamic and contractility data during different stages of ischaemia (mid after 20 min and late after 30 min) with no drug (Group C), milrinone (Group M) or dobutamine (Group D). Dobutamine was administered in medium dose after 20 min, and in high dose after 30 min of ischaemia. Data expressed as mean values (SD) of the mean. *P<0.05 compared with baseline period, in the same group. †P<0.05 compared with early ischaemic (without drug) period, in the same group. ‡P<0.05 compared with late ischaemic period (30 min), in the same group. HR, heart rate; SBP, systolic blood pressure; CO, cardiac output; SV, stroke volume; LVEDP, left ventricular end-diastolic pressure; LAD, left anterior descending; SVR, systemic vascular resistance

	Mid ischaemia (20 min)			**Late ischaemia (30 min)**		
	Control	**Milrinone**	**Dobutamine 10 μg kg^{-1} min^{-1}**	**Control**	**Milrinone**	**Dobutamine 20 μg kg^{-1} min^{-1}**
Haemodynamic variables						
HR (beats min^{-1})	83 (6)*	89 (7)†	89 (12)	87 (8)*	86 (6)	102 (10)†
SBP (mm Hg)	82 (12)	75 (16)	84 (11)	80 (12)	73 (12)	92 (8)
CO (litre min^{-1})	1.7 (0.5)*	2.1 (0.3)†	2.9 (0.7)†	1.9 (0.4)	2.2 (0.4)†	3.1 (0.7)†
SV (ml $beat^{-1}$)	21.0 (4.6)	23.2 (2.7)	32.9 (10.1)	22.2 (4.0)	26.4 (4.7)	28.4 (9.1)
LVEDP (mm Hg)	9 (3)*	8 (4)†	11 (2)*	10 (3)*	8 (5)†	10 (4)
LAD flow (ml min^{-1})	3 (1)*	6 (2)*	5 (2)*	4 (1)*	6 (2)*	6 (2)*
SVR (dyn s cm^{-5})	1762 (836)	1215 (397)†	1356 (113)	1434 (376)	1197 (400)†	1725 (500)*†
Contractility variables						
dP/dT (mm Hg s^{-1})	56 (12)	52 (14)	63 (10)	55 (10)	53 (9)	54 (6)
Emax (mm Hg ml^{-1})	3.8 (0.7)	4.4 (0.2)	4.4 (0.4)‡	3.8 (0.6)	4.4 (0.1)	5.0 (0.3)†

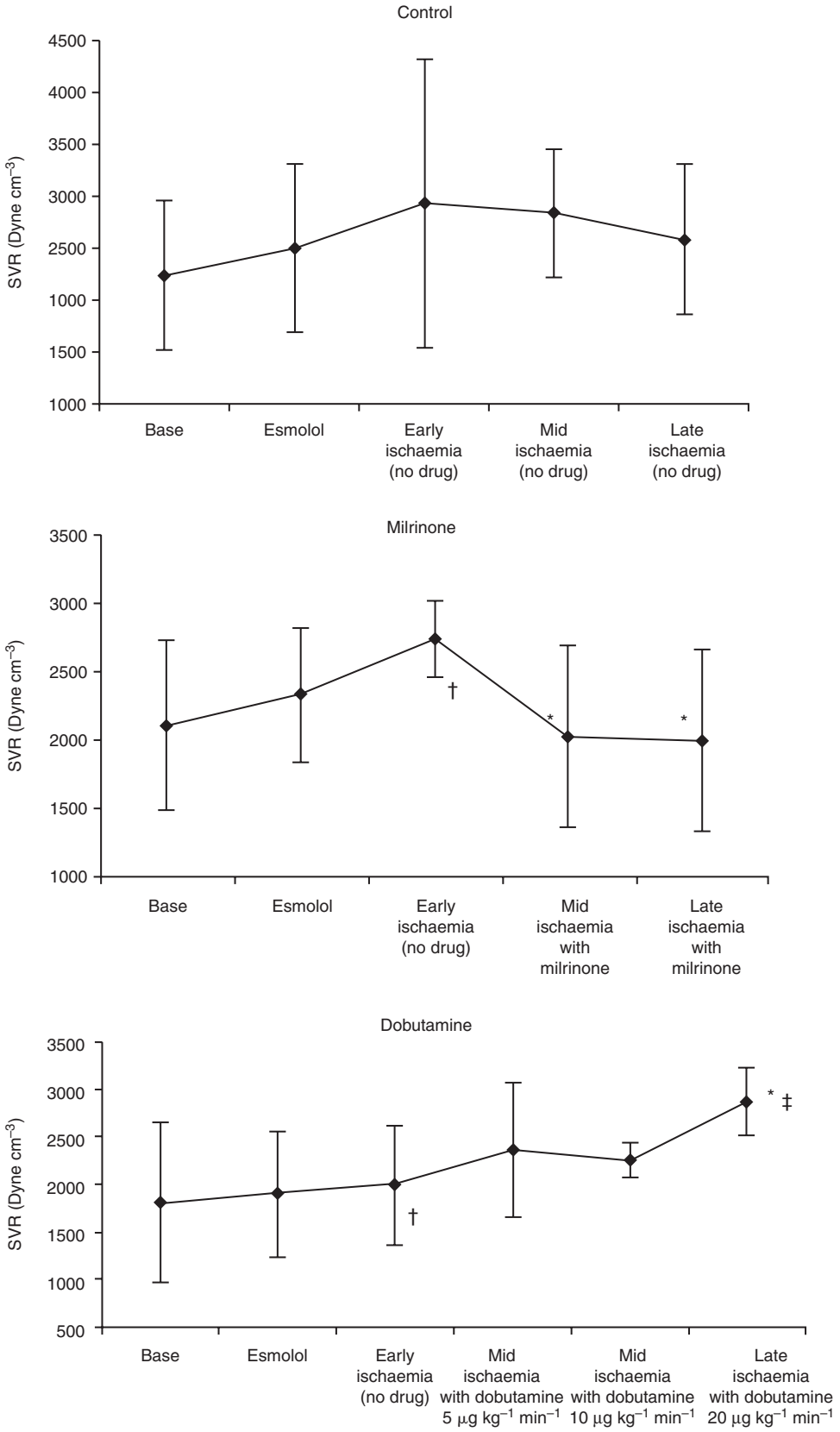

Fig 1 Calculated systemic vascular resistance (SVR) in different stages (baseline, esmolol, and ischaemia periods of 10, 20 and 30 min) with no drug (Group C), milrinone (Group M) or dobutamine (Group D). *P<0.05 compared with early ischaemia (without drug) period in the same group. †P<0.05 compared with late ischaemic period (30 min) in the same group. ‡P<0.05 compared with baseline period in the same group.

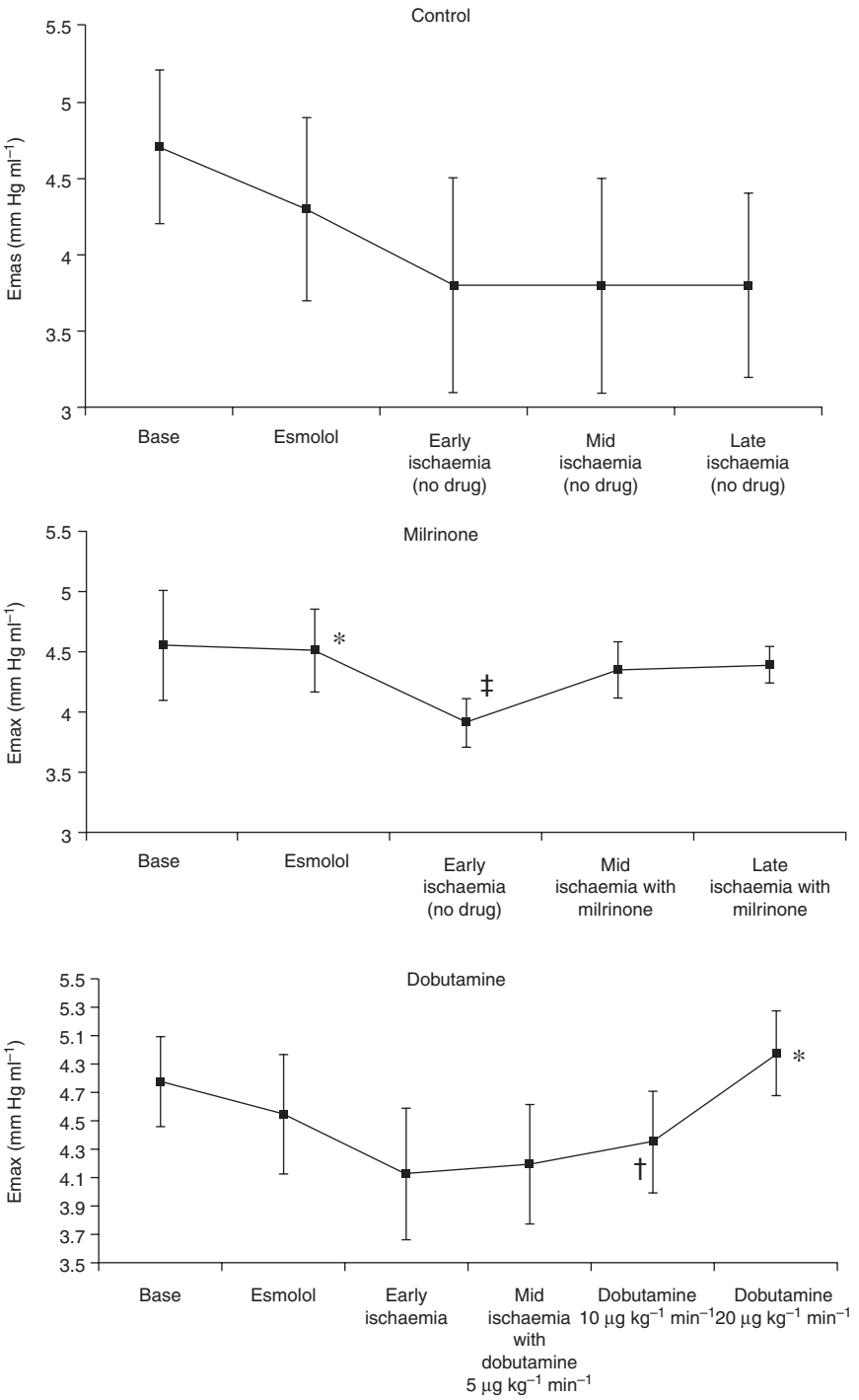

Fig 2 Measured contractility (Emax) in different stages (baseline, esmolol, ischaemic periods of 5, 10, 20 and 30 min) with no drug (Group C), milrinone (Group M) or dobutamine (Group D). Data expressed as mean values (SD) of the mean. *P<0.05 compared with early ischaemic (without drug) period in the same group. †P<0.05 compared with late ischaemic period (30 min) in the same group. ‡P<0.05 compared with baseline period in the same group.

dobutamine improved contractility, but under conditions that may exacerbate ischaemia.

Previous animal studies demonstrated that beta blockade can decrease lactate production and haemodynamic impairment caused by ischaemia, with relative preservation of endocardial blood flow.[20] The actual mass of lactate produced by the myocardium (negative value=production), which takes into consideration the arteriovenous lactate difference (as a percentage of the arterial value) and the blood flow into the area, was less (meaning better) during

ischaemia with esmolol.[27] Clinically, it has also been demonstrated that preoperative treatment with beta blockers will limit myocardial ischaemic damage and improve perioperative outcome.[28] In patients with severe left ventricular dysfunction undergoing major vascular surgery, the use of beta blockers is associated with a reduced incidence of in-hospital and long-term postoperative mortality.[29 30] Beta blockers are now standard treatment for mild to moderate heart failure.[6–9] However, because of myocardial ischaemia in patients with decreased left ventricular function, the associated depression in contractility caused by beta blockers may be significant.[31] Whilst many patients improve on beta blockade, some may deteriorate.[9]

The fact that esmolol did not have a significant effect on dP/dT is not surprising. The infusion was titrated to reduce HR by approximately 25%. It is well known that the negative inotropic and chronotropic effects of beta blockers are not necessarily parallel. In other words, beta blockers can produce a slight decrease in HR, but because they can also increase diastolic filling time, preload and contraction, these effects offset the mildly negative, inotropic effect of beta blockers. The end result will have only a minor effect on Emax (which is a better index of contractility than dP/dT), resulting in a non-statistically significant reduction in Emax.

The effect of beta blockade in this particular ischaemic model was well described and documented with esmolol administration, before and during induced ischaemia. Beta blockade before ischaemia was not involved in any haemodynamic changes or metabolic impairment when coronary artery occlusion was applied in the presence of existing beta blockade in pigs.[5] An esmolol infusion, given during a temporary LAD artery occlusion in dogs, preserved certain haemodynamic variables and the ratio of endocardial-to-epicardial blood flow, and decreased the apparent magnitude in lactate production.[31]

We recently addressed and evaluated separately the known protective effect of preoperative treatment with beta blockers in combination with the known protective effect of pre-ischaemic treatment with PDE inhibitors.[5] In a previous study, amrinone, with similar inotropic and vasodilatory properties, was demonstrated to have a protective metabolic effect, even in the presence of beta blockade with propanolol,[32] most likely on the basis of reversing myocardial depression. We also found that milrinone, in the presence of beta blockade, simultaneously changed supply and demand by reversing myocardial depression with increased supply and decreasing consumption as a result of decreased demand.[5] Decreased demand is an essential factor in many studies evaluating the protective effect of drugs or manipulations that demonstrate a positive effect on myocardial O_2 and lactate metabolism.[4 5 17–19] Beta blockade may attenuate the hypotensive and chronotropic effect of a PDEIII inhibitor but will not eliminate positive inotropism, the reduction in cardiac preload, or the increase in CO induced by milrinone.[13] Thus, the inotropic and haemodynamic effects of milrinone are preserved during beta blockade, and the mechanism of its action is probably independent of reflex adrenergic stimulation.[10] Moreover, when the combination of a PDE inhibitor and beta-blocking agent is administered long term in heart failure, their respective efficacies are additive and their adverse effects markedly reduced.[9] As mentioned earlier, the combination of a PDEIII inhibitor and beta blockade is still under investigation in a large multicentre, double-blinded, randomized trial, part of which has been disclosed.[7] The outcome of a prospective trial of milrinone for exacerbations of heart failure has already been published,[33] although the analysis was conducted only to determine the outcome in patients treated with or without beta blockade[6] and did not specifically examine the combination of PDEIII and beta blockade.

Beta-adrenergic agonists are commonly utilized to increase contractility. Dobutamine is used for diagnostic purposes during stress echocardiography. Dobutamine-induced wall motion abnormalities are independently associated with the increased risk of mortality and serious cardiac events, even in patients with normal baseline left ventricular function.[34]

Beta agonist effects may be less predictable in the presence of acute beta blockade. When dobutamine was administered to beta-blocked patients and compared with unblocked patients, there was no change in the cardiac index increase with the beta stimulant.[11] The vasoconstrictive response to dobutamine, however, was observed despite beta blockade,[9 11] in addition to the finding that beta agonists may not produce much of an increase in CO during full-dose beta blockade and may increase SVR via alpha-adrenergic stimulation.[8] PDEIII inhibitors, on the other hand, do not require interaction with beta receptors because of two factors: (i) the site of PDE inhibitor action is beyond the beta-adrenergic receptor pathway; and (ii) beta blockade reverses some of the desensitization phenomena that account for the attenuation of the PDE inhibitor response in heart failure related to upregulation in G (alphai), which are detrimental to the PDE inhibitor response.[8 9] Consequently, a PDE inhibitor will increase coronary flow and decrease wall stress in beta blockade, and thus, their use may result in a more favourable haemodynamic profile, while preserving the benefits of beta blockade.[11 14 15]

Our study in pigs has potential clinical applications, such as during off-pump myocardial revascularization when temporary coronary artery occlusion is performed. From our limited animal findings, it would appear that there may, theoretically, be some benefit for using milrinone in preference to other inotropic drugs in the presence of beta blockade. Milrinone administration should be considered in patients with acute ischaemic left ventricular dysfunction and preexisting beta blockade before using other inotropic drugs such as beta stimulants. Phosphodiesterase type III inhibitors may be considered before other inotropes in patients with coronary artery disease

who receive beta blockers, because they improve ventricular function and protect against myocardial ischaemia. Preexisting beta blockade has better protective properties when pretreated with milrinone since, in this combination, it simultaneously improves supply and decreases demand in the ischaemic myocardium.

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References

1 Ellis SG, Henschke CI, Sandor T, Synne J, Braunwald E, Kloner RA. Time course of functional and biochemical recovery of myocardium salvaged by reperfusion. *J Am Coll Cardiol* 1983; **1**: 1047–53

2 Kabela E, Barcenas L, Farah A. Effects of milrinone (Win 47203) on the coronary blood flow and oxygen consumption of the dog heart–lung preparation. *Am Heart J* 1986; **111**: 702–9

3 Sidi A, Pool JM, Rush W. Early administration of amrinone does not impair regional metabolism of O_2 or lactate and, by improving myocardial performance, preserves myocardial blood flow in the ischemic canine heart. *Anesth Analg* 1993; **76**: 1201–12

4 Sidi A, Rush W. Decreased regional lactate production and output due to intracoronary continuous esmolol during acute medium-to-high coronary stenosis. *J Cardiothorac Anesth* 1991; **5**: 237–42

5 Lobato EB, Botero M, Browd CR, Kirby DS, Sidi A. Effects of beta-blockade and PDEIII inhibition on myocardial ischemia and function during temporary coronary occlusion, abstracted. *Anesth Analg* 2001; **92**: S28

6 Gattis WA, O'Connor CM, Leimbergr JD, Felker GM, Adams KF Jr, Gheorghiade M. Clinical outcomes in patients on beta-blocker therapy admitted with worsening chronic heart failure. *Am J Cardiol* 2003; **91**: 169–74

7 Muhammad K, Ventura HO, Stapleton DD, Smart FW. Difficult cases in heart failure: Bridge to beta blockade in severe heart failure: the use of phosphodiesterase inhibitors. *Congest Heart Fail* 2000; **6**: 164–6

8 Bristow MR, Shakar SF, Linseman JV, Lowes BD. Inotropes and beta-blockers: is there a need for new guidelines? *J Card Fail* 2001; **7** (2 Supp1): 8–12

9 Lowes BD, Simon MA, Tsvetkova TO, Bristow MR. Inotropes in the beta-blocker era. *Clin Cardiol* 2000; **23** (3 Suppl): III1–16

10 Travill CM, Pugh S, Noble MI. The inotropic and hemodynamic effects of intravenous milrinone when reflex adrenergic stimulation is suppressed by beta-adrenergic blockade. *Clin Ther* 1994; **16**: 783–92

11 Tarnow J, Komar K. Altered hemodynamic response to dobutamine in relation to the degree of preoperative β-adrenoceptor blockade. *Anesthesiology* 1988; **68**: 912–19

12 Makela VHM, Kapur PA. Amrinone and verapamil-propanolol induced cardiac depression during isoflurane anesthesia in dogs. *Anesthesiology* 1987; **66**: 792–7

13 Lee KC, Canniff PC, Hamel DW, Pagani ED, Ezrin AM. Cardiovascular and renal effects of milrinone in beta-adrenoceptor blocked and non-blocked anaesthetized dogs. *Drugs Exp Clin Res* 1991; **17**: 145–58

14 Kim JH, Ham BM, Kim YL, *et al*. Prophylactic milrinone during OPCAB of posterior vessels: implication in angina patients taking β-blockers. *Eur J Cardiothorac Surg* 2003; **24**: 770–6

15 Kwak YL, Oh YJ, Kim SH, Shin HK, Kim JY, Hong YW. Efficacy of preemptive milrinone in off-pump coronary artery bypass surgery: comparison between patients with low and normal pre-graft cardiac index. *Eur J Cardiothorac Surg* 2004; **26**: 687–93

16 Omae T, Kakihana Y, Mastunaga A, *et al*. Hemodynamic changes during off-pump coronary artery bypass anastomosis in patients with coexisting mitral regurgitation: improvement with milrinone. *Anesth Analg* 2004; **101**: 2–8

17 Davis RF, Sidi A. The effect of isoflurane on the extent of myocardial necrosis and on systemic hemodynamics, regional myocardial blood flow, and regional myocardial metabolism in dogs after coronary artery occlusion. *Anesth Analg* 1989; **69**: 575–86

18 Sidi A, Gehrig RT, Rush W, Davis RF. Left-sided stellate ganglion ablation or "rate controlled" vagal nerve stimulation decreases regional myocardial metabolic impairment during acute ischemia in dogs. *J Cardiothorac Vasc Anesth* 1995; **9**: 50–8

19 Sidi A, Rush W. Adenosine for controlled hypotension: systemic compared with intracoronary infusion in dogs. *Anesth Analg* 1992; **75**: 319–28

20 Davis RF, DeBoer LW, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. *Anesth Analg* 1986; **65**: 711–17

21 Sidi A, Rush W, Davis RF. Regional myocardial metabolism and electrolyte balance during acute ischemia in dogs. *J Cardiothorac Anesth* 1988; **2**: 650–7

22 Sidi A, Davis RF. Lactate extraction fails to accurately reflect regional lactate production in ischemic myocardium. *J Cardiothorac Anesth* 1989; **3**: 321–8

23 Suga H. Left ventricular time-varying pressure-volume ratio in systole as an index of myocardial inotropism. *Jpn Heart J* 1971; **12**: 153–60

24 Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res* 1974; **35**: 117–26

25 Kass DA, Yamazaki T, Burkhoff D, Maughan WL, Sagawa K. Determination of left ventricular end-systolic pressure-volume relationships by the conductance (volume) catheter technique. *Circulation* 1986; **73**: 586–95

26 Miyahara K, Mikuniya A, Hanada H, Kanazawa T, Onodera K, Shinozaki N. Effect of inferior vena cava occlusion on left ventricular end-systolic pressure-volume relations in intact canine hearts—modulation by the autonomic nervous system. *Jpn Circ J* 1996; **60**: 652–61

27 Alousi AA, Canter JM, Fort DJ. The beneficial effect of amrinone on acute drug-induced heart failure in the anaesthetized dog. *Cardiovasc Res* 1985; **19**: 483–95

28 Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med* 1996; **335**: 1713–20

29 Feringa HH, Bax JJ, Schouten O, *et al*. Beta-blockers improve in-hospital and long-term survival in patients with severe left ventricular dysfunction undergoing major vascular surgery. *Eur J Vasc Endovasc Surg* Dec 13 [Epub ahead of print]

30 Schouten O, van Urk H, Feringa HH, Bax JJ, Poldermans D. Regarding "perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial". *J Vasc Surg* 2005; **42**: 825 (author reply 826)

31 Sidi A, Rush W, Davis RF. The influence of esmolol on myocardial metabolism, regional myocardial blood flow, acid–base, and electrolyte balance in dogs after acute coronary ligation. *Anesth Analg* 1988; **67**: 124–30

32 Gallagher KP, Kumada T, Koziol JA, McKown MD, Kemper WS, Ross J Jr. Significance of regional wall thickening abnormalities relative to transmural myocardial perfusion in anesthetized dogs. *Circulation* 1980; **62**: 1266–74

33 Cuffe MS, Califf RM, Adams KF, *et al*. Rationale and design of the OPTIME CHF trial: outcomes of a prospective trial of intravenous milrinone for exacerbation of chronic heart failure. *Am Heart J* 2000; **139**: 15–22

34 Elhendy A, Schinkel AF, Bax JJ, Van Domburg RT, Poldermans D. Prognostic value of dobutamine stress echocardiography in patients with normal left ventricular systolic function. *J Am Soc Echocardiogr* 2004; **17**: 739–43