Combined therapy with dobutamine and omecamtiv mecarbil in pigs with ischemic acute heart failure is attributed to the effect of dobutamine

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Running title: Dobutamine plus omecamtiv for acute heart failure

Abstract

Inotropic support in ischemic acute heart failure is controversial. We tested a therapeutic principle for acute heart failure by combining a low dose of omecamtiv mecarbil (OM; 0.25 mg/kg bolus plus 0.25 mg/kg/h) with a low dose of dobutamine (Dobut; 1.25 µg/kg/min). In 10 pigs subjected to myocardial ischemia by left coronary microembolization, this cotreatment increased cardiac power (CP) from 0.48 ± 0.14 to 0.81 ± 0.22 W ($p < 0.05$). When the drugs were given as a monotherapy, CP increased from 0.57 ± 0.11 to 0.65 ± 0.15 W (OM; n=5; not significant) and from 0.40 ± 0.07 to 0.70 ± 0.10 W (Dobut; n=5; $p < 0.05$). Dobut counteracted OM-mediated impairments in early relaxation and diastolic shortening. In a second protocol using the same doses, we assessed cardiac efficiency in five healthy pigs by relating myocardial oxygen consumption (MVO_2) to the pressure-volume area. Here, the increases in cardiac work and MVO_2 were matched, leaving cardiac efficiency unaltered by this drug combination. Low-dose cotreatment with OM+Dobut produces an appropriate hemodynamic effect with improved CP at doses that do not affect cardiac efficiency. This outcome is mainly attributed to the inotropic effect of dobutamine.

Keywords: acute heart failure, inotrope, diastole, cardiac efficiency

Introduction

The use of inotropic support in ischemic acute heart failure (AHF) is controversial. The ESC guidelines give the weakest recommendation (class IIb) at the lowest level of evidence (C) for such treatment[1]. The reluctance stems from the well-known arrhythmogenic effects[2], increased myocardial energy demands[3] and elevated mortality seen in clinical trials following inotrope therapy[4]. The adverse events are particularly prominent at a high dosage, which is often necessary to reach desired treatment goals. AHF patients typically have a previous history of cardiovascular disease (CVD), with impaired sensitivity in the adrenergic pathway[5] and/or are on oral beta blockers at hospital admission[1]. These challenges have led to R&D for new inotropes that do not act on the adrenergic cAMP-mediated pathway. A leading drug in this pipeline is the myosin activator omecamtiv mecarbil (OM), which is currently under investigation in a phase III trial, GALACTIC-HF[6]. OM prolongs the systolic ejection time[7], which shortens diastole[8]. This finding has raised concerns related to ventricular filling[8] and myocardial blood flow[9] that are supported by elevated troponins in clinical trials[10,11]. Additionally, continuous activation of myosin ATPase by OM[7] causes substantial myocardial oxygen wastage when OM is given as a monotherapy for experimental AHF[12].

We aimed to assess the therapeutic efficacy of a low-dose cotreatment with omecamtiv mecarbil and dobutamine (OM+Dobut) in a pig model of ischemic AHF. We hypothesize that the drugs potentiate systolic unloading and limit the adverse events observed with both drugs at high dosages. Outcome was assessed by surrogate endpoints such as systolic unloading, diastolic relaxation, pressure-volume relations and myocardial oxygen consumption (MVO_2).

Methods

Experimental animals

All experiments were conducted in accordance to the Consensus Author Guidelines for Animal Use developed by The International Association of Veterinary Editors (IAVE). A total of 15 castrated male domestic pigs (Sus scrofa domesticus) weighing 25.7 ± 2.0 kg (mean ± SD) were employed. The animals were held in an approved animal facility as previously described[8].

General instrumentation

Induction of anesthesia, intubation and general instrumentation for all animals is described elsewhere[8].

Closed-chest model of ischemic acute heart failure

Coronary microembolization is a reliable and clinically relevant method to induce ischemic ventricular dysfunction[13]. In the present study we used a protocol as previously described[14]. Throughout the experiments, continuous infusion of 0.9% NaCl (10 ml/kg/h) was administered to maintain the circulating volume. Glucose (1.25 g/l) was added to the infusion to maintain blood glucose levels. After general instrumentation, a Swan-Ganz catheter was placed in the pulmonary trunk for assessment of central venous and pulmonary arterial pressure, as well as cardiac output (CO) by thermodilution. Right femoral artery was cannulated to enable catheterization of left coronary artery main trunk and the following coronary microembolization protocol. Transthoracic short-axis echocardiography (Vivid I, GE, USA) was used for calculations of left ventricular (LV) volumes.

Open-chest model for the assessment of cardiac energetics

The open-chest model is previously described in our group[15]. Healthy pigs were employed to assess cardiac energetics. Due to increased fluid loss in this open-chest model, a higher NaCl 0.9% volume was infused (20 ml/kg/h). Glucose (1.25 g/l) was added to the infusion to maintain blood glucose levels. After general surgical preparation, we advanced with 1) median sternotomy, 2) pericardial removal, 3) hemiazygos vein ligation, 4) dissection to free the pulmonary trunk, 5) dissection to free the coronary arteries, 6) suture of three sonomicrometric crystals (Sonometrics Corporation, Canada) into the myocardium, and 7) great cardiac vein catheterization via the superior vena cava using a pediatric central venous catheter (Arrow 24G; eSutures, USA). Thereafter, flow probes (Medistim, Norway) were placed around the main pulmonary- and coronary arteries (right branch, circumflex and left anterior descending) for measurements of CO and coronary blood flow, respectively. The sonomicrometric crystal dimensions (apex to basoseptal and basolateral to basoseptal) were calibrated to endocardial LV dimensions from epicardial echocardiography (Vivid I, GE, USA).

Experimental protocol

After surgical preparation and stabilization in the closed-chest protocol (n=10), baseline recordings were performed before LV ischemia by coronary microembolization was induced as described previously[8]. Level of ischemic acute heart failure was aimed at reduction in the stroke volume by approximately 30% and the pulmonary capillary wedge pressure rise to 15-20 mmHg. An average of 16.1 ± 6.3 ml of microspheres was injected to reach this level of heart failure. Second recordings were performed approximately 30 minutes after the last injection under stable hemodynamics. The animals were then randomly divided into two groups to receive either Dobut

(1.25 µg/kg/min) (n=5) or OM (0.25 mg/kg bolus plus 0.25 mg/kg/h) (n=5) as the first treatment. Monotherapy recordings were performed 30 minutes after the start of drug infusion. The second drug was added for combination therapy, and final recordings were carried out after 30 minutes of infusion.

A group of healthy animals (n=5) was employed for the assessment of cardiac energetics. We performed an open-chest surgical preparation as described above before baseline recordings. Dobut (1.25 µg/kg/min) was infused for 30 minutes before new recordings, and OM (0.25 mg/kg bolus plus 0.25 mg/kg/h) in combination with Dobut was infused before the next recordings. Dobut was then withdrawn before final measurements after 30 minutes of OM infusion alone. Finally, the left ventricle was weighed after euthanasia by intravenous pentobarbital sodium injection. Euthanasia was performed according to the regulations on the use of animals in experiments (Norwegian legislations).

Left ventricular energetics

Cardiac efficiency was assessed by relating left ventricular work (pressure-volume area, PVA) to MVO_2 at multiple workloads. Multiple workloads were achieved by a stepwise reduction in preload by inflating a balloon catheter situated in the vena cava as previously described[12]. Calculation of PVA and MVO_2 is described in detail elsewhere[3,12].

Hemodynamics

Methods for pressure, flow and CO measurements are described earlier by our research group[8]. All LV volumes were calculated using the bullet formula[16], where

Volume = 5/6 x Area x Length.

End-diastolic and end-systolic areas were measured with short-axis transthoracic echocardiography, and the long-axis diameter (length) was calculated as 1.37 times the short-axis diameter obtained by echocardiography[17].

For the closed-chest model, values from transthoracic echocardiography were used to calculate the volumes. For the open-chest model, endocardial end-diastolic diameters were obtained at steady-state hemodynamics before preload reductions using epicardial echocardiography for the calibration of the sonomicrometric crystal-derived short-axis dimension. Dimensions from crystal signals were used for volume estimations with the same formula (bullet) at each preload. Hemodynamic data was recorded and analyzed using ADI labchart software (ADI, New Zealand).

Statistical analysis

Power analysis (G*Power) was carried out, and results from previous studies were considered to estimate the number of animals needed. Calculations and statistical analyses after the experimental protocols were performed using a spreadsheet (Microsoft Excel, Microsoft, USA) and a statistical package (GraphPad Prism 7, GraphPad, USA). Values are presented as the mean ± standard deviation (Figures 2-4). Repeated measure one-way ANOVA followed by Tukey's test for multiple comparisons was used on bar graphs in Figures 3 and 4. Analyses of covariance (ANCOVA) were used on cardiac energetics data (linear regression Figure 4). P-values < 0.05 were regarded as statistically significant.

Results

Inducing myocardial ischemia by coronary microembolization substantially impaired systolic function as seen by a halving of end-systolic elastance and preload recruitable stroke work (Figure 3 G and H). This led to ventricular dilatation (Figure 3 B), rightward shift of the pressure-volume relationship (Figure 2) and reduced cardiac output (Figure 3 D). Monotherapy with OM did not restore systolic function in the ischemic hearts (Figures 2 and 3 B-H). However, its impact on the heart was recognized by characteristic prolongations of systolic ejection time and impaired early relaxation (SET and Tau; Figure 3 E and F). Low-dose Dobut as monotherapy did restore systolic function as seen by a normalization of the pressure-volume relationship (Figure 2 and 3 B), and that cardiac output increased to preischemic levels (Figure 3 D). Also, Dobut restored early relaxation as seen by a normalization of Tau (Figure 3 F).

The relationship between total left ventricular work and MVO_2 was measured in five non-ischemic pigs. As seen from the overlapping confidence interval, none of the drug protocols had impact on this relationship over a broad range of cardiac workload (Figure 4 left panels). This suggests that cardiac efficiency was maintained during all treatments and not depending on workload. At steady-state workload (Figure 4 right panels) both MVO_2 and cardiac output increased when OM and Dobut was combined.

Discussion

Effect of the drugs on the ischemic heart

The OM dose selected in the present study is comparable to that used in the ATOMIC-HF trial[11] for the treatment of AHF. Although this phase II trial did not reach its primary endpoints, i.e.

dyspnea relief, the treatment did improve cardiac function by moderately decreasing LV systolic dimensions. Such systolic unloading was not seen in the present study using pigs subjected to ischemic acute heart failure. This discrepancy could not be explained by different sensitivity to OM between humans and pigs since the functional signature of the drug (prolongation of SET) was comparable. More likely, the further impairment of diastolic function in the ischemic ventricle by OM counteracted any systolic improvement in the present study. In contrast, low-dose Dobut monotherapy did, to a large extent, restore cardiac function back to preischemic levels. This is in line with others giving dobutamine to dogs also subjected to coronary microembolization[13]. When the drugs were combined, minimal additive effects were observed compared to administration of Dobut alone. However, the combination was well tolerated, and this dual treatment restored cardiac power (CP) to preischemic levels (Figure 3 C). This is clinically important because CP is the superior early survival predictor in patients hospitalized with cardiogenic shock[18], and *in vivo* animal experiments can help guide further clinical and pre-clinical studies. Of interest was that Dobut counteracted the unwanted effects of OM on diastole. This is evident by a normalization of relaxation rate and a relatively prolonged filling time by shortening the SET. However, a chronotropic effect was seen by this combination treatment that may be a limitation when treating patients with tachycardia. To our knowledge, this is the first study to assess this dual inotropic drug target approach for improving systolic function in the ischemic heart.

Impact of the drugs on cardiac efficiency

An attempt to use OM as a sole drug in experimental AHF revealed that the drug caused substantial myocardial oxygen wastage that was suggested to be mediated by hyperactivity in

myosin ATPase[12]. Such trends were also observed in a study that gave OM to conscious dogs[19]. Here, a mismatch of 33% increase in MVO_2 versus only a 22% increase in CO was observed following 24 hours of drug infusion[19].

However, catecholamines also cause myocardial oxygen wastage, particularly prominent in high doses[20]. This oxygen wastage is likely mediated by a metabolic switch towards myocardial fatty acid oxidation[21] as well as altered intracellular calcium handling[3]. However, during low-dose Dobut infusion, such oxygen waste is not clear[20].

In the present study, we did not observe any significant alteration in cardiac efficiency by the selected low dose of Dobut, by the low dose of OM, or when the drugs were combined. When OM and Dobut were combined, the heart responded with a matched increase in MVO_2 and CO. Additionally, when using gold standard methodology (PVA-MVO_2 relationship), there was no indication of surplus MVO_2 for any of the interventions. This was seen by that data obtained during treatment substantially overlapped with baseline recordings over a broad range of cardiac workloads.

Effect of the drugs on myocardial perfusion

Concerns have been raised regarding the safety of OM in relation to myocardial perfusion[9]. The drug prolongs systole, increases MVO_2[12], and reduces relaxation speed[8], which may underlie the cardiac troponin elevation observed in two clinical trials[10,11]. Our study did not show any indication of myocardial malperfusion when OM was combined with Dobut. Blood gas analysis showed that the oxygen saturation in blood drained from the great cardiac vein was never below 21%, and myocardial lactate uptake was present at all measurement points (range

0.95 – 1.74 g/min). However, a net global lactate uptake in the myocardium does not exclude regional lactate release from ischemic regions[22].

Limitations

Our study was carried out in healthy juvenile pigs, which are different from typical AHF patients with old age and a previous history of CVD. An animal model in which coronary perfusion is truly challenged, such as coronary stenosis and tachycardia, is warranted to gain the necessary knowledge on the safety of this cotreatment scheme in ischemic heart disease. Additionally, the timeframe of this study is shorter than the typical clinical time course of AHF. This precludes the use of troponin as a quantitative measure of myocardial damage in this study. This is unfortunate since elevated troponin is observed in clinical trials using omecamtiv. Also, activation of lipoprotein lipase and the subsequent initiation of fatty acid metabolism by adrenergic stimulation occurs over time. Thus, a longer study period using this cotreatment protocol for assessing cardiac efficiency is warranted.

Cardiac energetics was not assessed in a heart failure model like the coronary microembolization cohort. The rationale to use a separate non-ischemic protocol is, by our experience, the most sensitive setup to detect any surplus MVO_2.

The closed chest AHF cohort aims to reassemble the clinical setting of patients admitted to the ICU with ischemic acute heart failure. Sternotomy and the following cardiac instrumentation as required for assessing energetics is a considerable surgical trauma. This impacts general hemodynamics, thus an induction of severe myocardial ischemia in addition to this often leads to hemodynamic collapse in the need for inotropes. This would preclude the pre-drug measurements.

Further, ischemia is often complicated with episodes of arrhythmia. This limits the accuracy of the PVA-MVO_2 recordings substantially. Also, the accuracy of the work independent assessment of energetics by regression analysis is dependent on the range of workloads. This is carried out in an unloading protocol by restricting venous return. A compromised circulation (i.e. AHF) does not allow much unloading before organ malperfusion sets in.

Previously, our group have documented that therapeutic levels of omecamtiv impacts cardiac efficiency quantitatively similar in both preischemic and ischemia-reperfusion induced acute heart failure[12]. Thus, the fact that no impact on cardiac efficiency was seen in an optimized preischemic model, we see it as highly unlikely that this conclusion would differ in an AHF model. Finally, this study assessed the therapeutic effects using only single doses. This may hamper a general qualitative statement on the potential of this therapy in the clinical setting.

Conclusions

Combination treatment with low-dose omecamtiv mecarbil and dobutamine is well tolerated in the ischemic heart. This drug combination does not aggravate cardiac efficiency, as it does not alter the MVO_2-work relation. However, the data does not support our hypothesis that this cotreatment potentiates systolic function, as the restoration of cardiac function is almost exclusively ascribed to the inotropic effect of dobutamine.

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Conflicts of interest

None declared.

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Figure legends

Figure 1.

Schematic diagram summarizing the two protocols used. OM, Omecamtiv Mecarbil (0.25 mg/kg bolus plus 0.25 mg/kg/h); Dobut, dobutamine (1.25 µg/kg/min).

Figure 2. Pressure-volume relations from ischemic acute heart failure pigs.

Left ventricular (LV) end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR) in healthy pigs (black) subjected to ischemic acute heart failure by left coronary microembolization (gray). The left panel shows data from five pigs in which dobutamine (Dobut; yellow) was given as the first treatment. The middle panel shows five pigs in which omecamtiv mecarbil (OM; blue) was given first. In both groups, the second inotrope was subsequently added for the assessment of OM+Dobut cotreatment (green). The right panel shows data for both groups together with an illustration of LV pressure-volume loops. All data are presented as the mean ± standard deviation.

Figure 3. Hemodynamic indices from ischemic acute heart failure pigs.

Following baseline recordings (stripe), the animals were subjected to left ventricular (LV) ischemia (blank) by coronary microembolization. The pigs received either dobutamine (Dobut; n=5, gray, left stack) or omecamtiv mecarbil (OM; n=5, gray, right stack) as the first drug. The second drug was subsequently added for final recordings of the cotreatment (OM+Dobut; black).

HR, heart rate; ESV, end-systolic volume obtained by transthoracic echocardiography of the LV short axis; CP, cardiac power is cardiac output multiplied by LV developed pressure; CO cardiac output measured by thermodilution; SET, systolic ejection time is the time between peak positive and peak negative derivatives of LV pressure (dP/dt_{max} and dP/dt_{min}, respectively); Tau, the time constant of LV isovolumetric relaxation calculated by Weiss's method; PRSW, preload recruitable stroke work is the slope of the relation between end-diastolic volume and stroke work during rapid preload reductions; Ees, end-systolic elastance is the slope of the end-systolic pressure-volume relation. Bars indicate mean values with standard deviations. Brackets indicate statistical significance. P-values < 0.05 were considered statistically significant.

Figure 4. Cardiac energetics in healthy pigs.

Cardiac efficiency data from 5 pigs at baseline (striped bar, solid line), after receiving dobutamine (Dobut; gray bar, dotted line), after adding omecamtiv mecarbil (OM+Dobut); black bar, dotted line), and after withdrawal of Dobut (OM; gray bar, dotted line). Left panels show regression lines including 95% confidence intervals of the relationship between left ventricular oxygen consumption (MVO_2) and total mechanical work (pressure-volume area, PVA) at multiple workloads. At each timepoint, 7-9 recordings of the PVA-MVO_2 relationship were carried out by a stepwise reduction in preload. None of the regressions were significantly different. The right panels show steady-state MVO_2 and cardiac output measurements from the same pigs at each intervention. Values are presented as the mean ± standard deviation.

Figure 1.

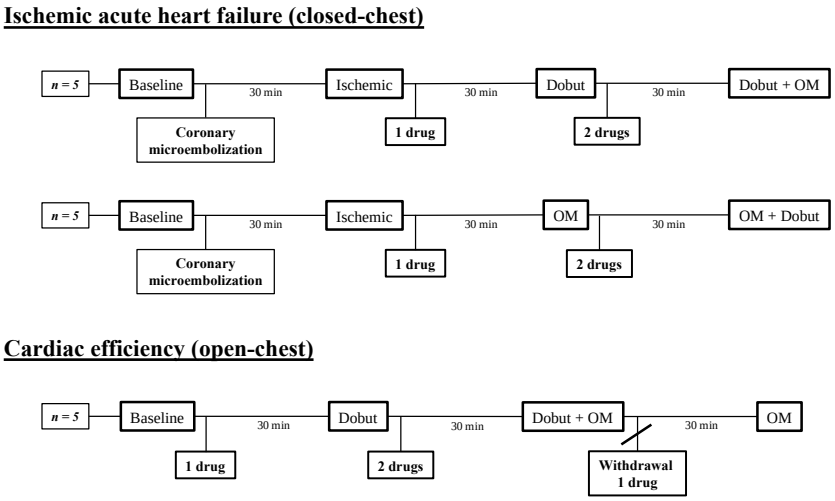

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Figure 2.

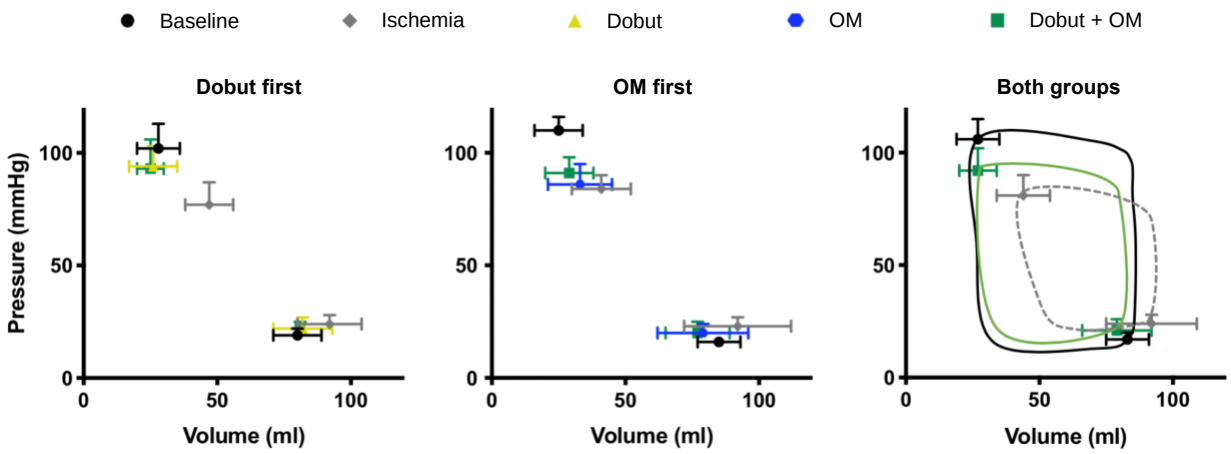

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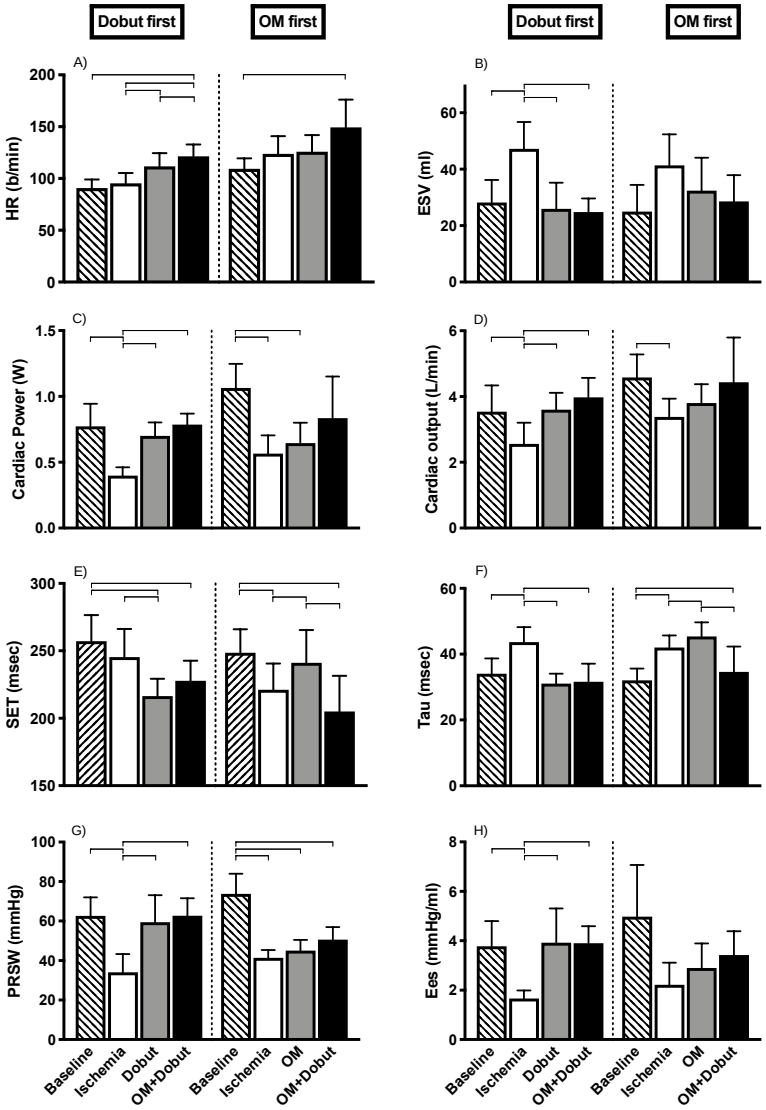
Figure 3.


Dobut first
OM first
Dobut first
OM first
A)
B)
HR (b/min)
ESV (ml)
C)
D)
Cardiac Power (W)
Cardiac output (L/min)
E)
F)
SET (msec)
Tau (msec)
G)
H)
PRSW (mmHg)
Ees (mmHg/ml)
Baseline
Ischemia
Dobut
OM+Dobut
Baseline
Ischemia
OM
OM+Dobut
Baseline
Ischemia
Dobut
OM+Dobut
Baseline
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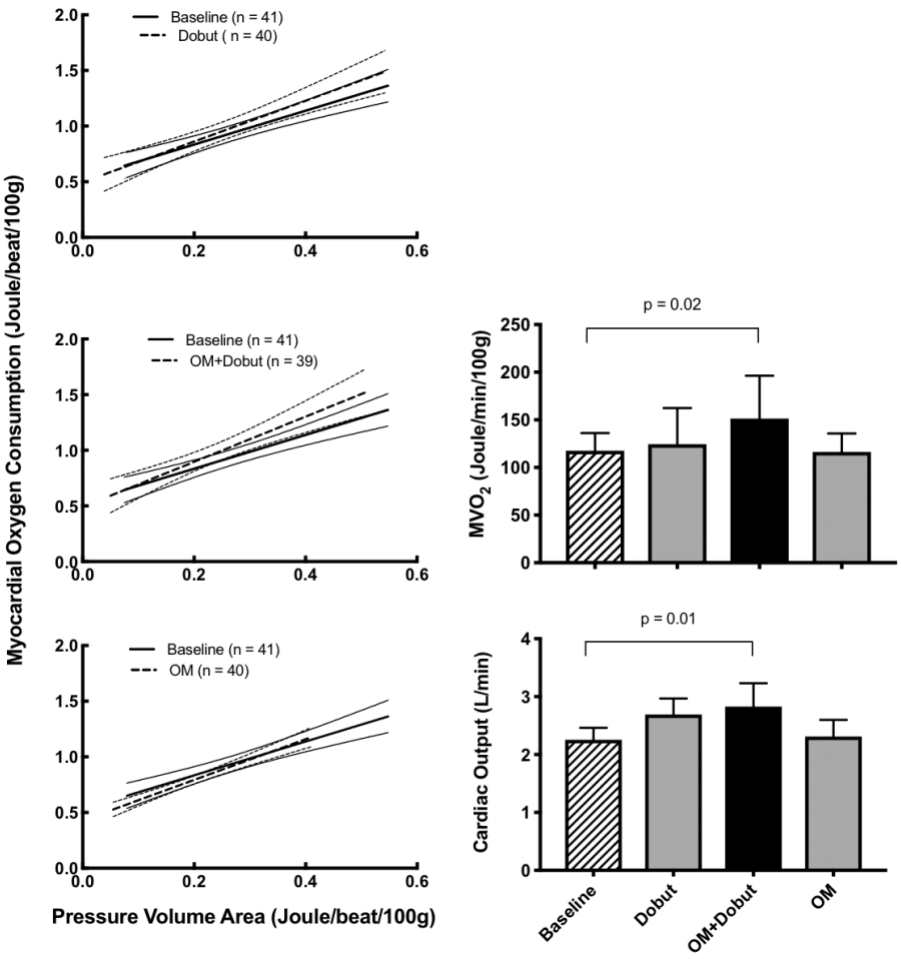
OM
OM+Dobut

Figure 4.


Baseline (n = 41)
Dobut (n = 40)
Baseline (n = 41)
OM+Dobut (n = 39)
Baseline (n = 41)
OM (n = 40)
Myocardial Oxygen Consumption (Joule/beat/100g)
Pressure Volume Area (Joule/beat/100g)
p = 0.02
MVO2 (Joule/min/100g)
p = 0.01
Cardiac Output (L/min)
Baseline
Dobut
OM+Dobut
OM

403