# Stimulation of $Rb^+$ Uptake by Dobutamine in Pig Hearts *in vivo* Assessed by $^{87}$Rb-MRS

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## Introduction

We have previously shown using $^{87}$Rb MRI that the adrenergic agonist, dobutamine (Dob) greatly stimulated $Rb^+$ uptake (~2.5 fold) in isolated crystalloid-perfused pig hearts under constant flow conditions [1]. In addition, our experiments *in vivo* showed that pig hearts can be safely loaded with $Rb^+$ over 60-min period, however the $Rb^+$ uptake kinetics was relatively slow [2]. In the present work we studied whether Dob can increase $Rb^+$ uptake rate *in vivo* to shorten the loading period without significant side effects.

## Methods

*Pig model*. Domestic pigs (33.6±2.9 kg, n = 8) were anesthetized with 1.5-2.0% isoflurane in oxygen via inhalation mask. Following median sternotomy the heart was exposed and a surface coil placed against the anterior left ventricular wall. The right femoral vein and artery were cannulated for *iv* RbCl infusion and taking arterial blood samples and monitoring blood pressure, respectively. Baseline hemodynamic parameters were: heart rate (HR), 106±9 bpm, systolic pressure (SP), 78±7 mmHg, diastolic pressure, 40±3 mmHg. Baseline blood parameters were: $pO_2$, 334±57 mmHg, pH, 7.43±0.03, glucose, 5.5±1.1 mM, lactate 1.1±0.3 mM, hematocrit, 27±5%, hemoglobin, 8.4±1.0 g/dL.

*Experimental protocol*. RbCl (188 mM) was infused at a rate of 4 mL/min (1.35±0.14 mmol/h/kg) simultaneously with Dob (0.6 mg/h/kg) over 60-min period. $^{87}$Rb MR spectra acquisition started simultaneously with RbCl infusion and lasted 120 min. Blood samples were taken periodically over the 120-min period. Thereafter the heart was arrested by an intra-ventricular injection of KCl, and excised. Samples of heart, skeletal muscle, liver, kidney and lungs were taken to determine $Rb^+$ content.

*$^{87}$Rb MRS*. The spectra were acquired every 5 min on a Bruker Avance spectrometer interfaced to a Magnex 7T, 40-cm horizontal bore magnet using a 80 μs pulse applied every 10 ms with NA = 10,000 and sweep width of 20 KHz. Following exponential multiplication (LB = 150 Hz) FIDs were Fourier transformed and peak heights and areas were calculated. Rb contents in tissue and blood plasma samples were determined by $^{87}$Rb MRS using a Bruker AM-360 spectrometer with a vertical bore magnet.

## Results

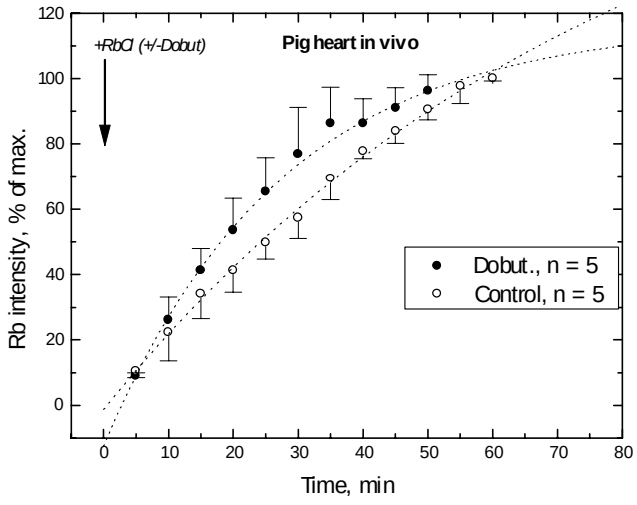
Dob increased the rate of rise in $Rb^+$ signal intensity (Fig) due to increase in the rate constant ($kx10^3$, $min^{-1}$) and stimulation of $Rb^+$ uptake, despite lower plasma levels and molar fractions ([Rb]/([Rb]+[K]), Table) of [$Rb^+$] between 10 and 30 min of loading. HR and SP increased to 161±15 bpm (+52%) and 93±11 mmHg (+19%) by Dob, while the rest of the parameters remained unchanged.

| Group | Parameter | | | | |
|---|---|---|---|---|---|
| | $kx10^3$ | Flux, %/min | Plasma [$Rb^+$], mM | Plasma $Rb^+$, mol. fr.,% | Flux/mol. fr., $min^{-1}$ |
| 1. Dob | 36±11.7 | 4.8 | 0.51±0.19 | 9.3±2.8 | 0.51 |
| 2. Control [2] | 13±2.4 | 2.5 | 0.73±0.24 | 13.3 | 0.19 |

Termination of infusion over 60-min period reduced $Rb^+$ intensity to 67±5 and 65±7% (5.2±0.9 and 4.8±1.6 mmol/kg) of the maximum (~7.6 mmol/kg) in the control and Dob groups, respectively. At the end of the experiment cardiac/plasma Rb ratio was 39±7.8 and 38±9.2 in the control and Dob groups, respectively, assuming intracellular water content of 0.5 L/kg.

## Discussion

The increase in the $Rb^+$ uptake rate by Dob (2-2.5-fold) in cardiac muscle can be explained by adrenergic stimulation of the $Na^+/K^+$ ATPase. Indeed, we observed previously in isolated pig hearts 2.5-fold increase in the $Rb^+$ uptake rate induced by Dob [1] in the absence of changes in HR and blood flow. However under *in vivo* conditions Dob increased HR by 52%, which could contribute to the increased $Rb^+$ uptake due to more frequent opening of $K^+$ channels and acceleration of $K^+$ turnover. In addition, elevation of blood pressure by 19% (+ vasodilatation) doubled coronary blood flow [3], which might contribute to stimulation of $Rb^+$ uptake due to increased $Rb^+$ supply rate. However dependence on flow is not linear, since 65% increase in flow was associated with 20-30% increase in $Rb^+$ uptake rate [4]. Thus Dob activates $Rb^+$ uptake via adrenergic stimulation of $K^+$ turnover and increased coronary flow.




## References

1. Kupriyanov et al., *MRM*, 2002;**48**:15-20.
2. Kupriyanov et al., *Proc Intl Soc Mag Res Med*, 2003;**11**:1708.
3. Kupriyanov et al., manuscript in preparation.
4. Kupriyanov et al., *MRM*, 2003;**49**:99-107.