Supplemental Data

Acute hemodynamic effects of inhaled sodium nitrite in pulmonary hypertension associated with heart failure with preserved ejection fraction

Short title: Inhaled nitrite in PH-HFpEF

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Abbreviation	Legend	Units
RA	Right atrial pressure	mm Hg
RVS	Right ventricular systolic pressure	mm Hg
RVD	Right ventricular diastolic pressure	mm Hg
PAS	Pulmonary artery systolic pressure	mm Hg
PAD	Pulmonary artery diastolic pressure	mm Hg
mPAP	Mean pulmonary artery pressure	mm Hg
PCWP	Pulmonary capillary wedge pressure	mm Hg
TPG	Transpulmonary gradient	mm Hg
DPG	Diastolic pressure gradient	mm Hg
CO	Cardiac output	L/min
CI	Cardiac index	$L/min/m^2$
TPR	Total pulmonary resistance	mm Hg/L/min
PVR	Pulmonary vascular resistance	mm Hg/L/min
HR	Heart rate	Beats per min
C pa	Pulmonary artery compliance	mL/mm Hg
SBP	Systolic blood pressure (systemic)	mm Hg
DBP	Diastolic blood pressure (systemic)	mm Hg
Mean BP	Mean blood pressure (systemic)	mm Hg
C sys	Systemic arterial compliance	mL/mm Hg
SVR	Systemic vascular resistance	mm Hg/L/min
PVR/SVR	Ratio of PVR to SVR	NA
O2 sat	Peripheral oxygen saturation (by pulse oximeter)	%
Meth. Hgb	Methemoglobin	%

Table E1. Distribution of variables prior to administration of inhaled nitrite (baseline 2). Each cell indicates the median (IQR).

	PH-HFpEF	**Group 1 PAH**	**Group 3 PH**	P value for overall difference
RA	11 (9-12)	4 (3-8)	6 (4-9)	0.008
RVS	54 (47-58)	65 (57-75)	61 (60-63)	0.052
RVD	16 (13-18)	6 (4-10)	11 (9-12)	0.008
PAS	56 (38-64)	71 (55-75)	64 (62-67)	0.09
PAD	24 (19-29)	26 (18-28)	27 (23-30)	0.4
mPAP	33.6 (28.0-38.3)	40.5 (28.9-43.5)	39.9 (36.0-41.0)	0.4
PCWP	18 (16-20)	7 (7-12)	12 (11-15)	<0.001
TPG	13.0 (11.0-19.3)	28.5 (22.0-31.3)	27.4 (25.0-32.0)	0.011
DPG	5 (0-10)	14 (9-16)	16 (12-19)	0.012
CO	5.8 (4.6-6.2)	5.0 (4.1-6.3)	6.2 (4.2-6.5)	0.5
CI	2.5 (2.4-2.8)	2.7 (2.3-3.1)	3.1 (2.2-3.1)	0.6
TPR	6.7 (4.3-7.2)	6.8 (5.9-9.8)	6.7 (6.0-7.1)	0.8
PVR	2.7 (2.0-3.2)	4.6 (4.3-5.6)	4.4 (4.3-4.9)	0.006
HR	68 (62-75)	68 (60-71)	84 (75-95)	0.012
C pa	2.8 (2.1-3.8)	2.0 (1.4-2.4)	1.9 (1.6-2.4)	0.030
SBP	136 (120-145)	112 (106-121)	137 (122-142)	0.002
DBP	69 (56-75)	67 (62-75)	74 (70-77)	0.4
Mean BP	90 (75-102)	84 (79-90)	94 (92-100)	0.07
C sys	1.27 (1.11-1.43)	1.70 (1.16-2.04)	1.11 (0.81-1.58)	0.037
SVR	14.3 (9.6-20.4)	16.1 (12.0-20.0)	15.0 (14.1-17.9)	0.8
PVR/SVR	0.17 (0.14-0.33)	0.36 (0.26-0.46)	0.31 (0.25-0.35)	0.025
O2 sat	98 (96-99)	97 (94-99)	95 (94-98)	0.3
Meth. Hgb	0.8 (0.6-1.1)	0.8 (0.6-1.0)	1.0 (0.9-1.3)	0.5

Table E2. Effect of intervention on study variables across all time points. Each cell indicates the β (mean change of variable, and 95% CI) during the intervention compared to the baseline measure (with associated P value) from mixed effect model. Variables requiring transformation are noted.

	PH-HFpEF	**Group 1 PAH**	**Group 3 PH**	P value for interaction of groups	P value for PH-HFpEF vs Group 1	P value for Group 3 vs 1	P value for PH-HFpEF vs Group 3
RA (square root)	-1.05 (-1.27- -0.83) P <0.001	-0.46 (-0.71- -0.22) P <0.001	-0.65 (-1.08- -0.22) P = 0.003	0.005	0.001	0.4	0.1
RVS	-10.4 (-13.1- -7.7) P <0.001	-2.0 (-6.6- 2.6) P = 0.4	-4.4 (-7.9- -0.7) P = 0.018	0.025	0.012	0.6	0.06
RVD	-6.8 (-9.6- -4.0) P <0.001	-2.2 (-3.9- -0.5) P = 0.013	-2.6 (-7.6- 2.4) P = 0.3	0.031	0.018	0.7	0.018
PAS	-9.9 (-12.3- -7.4) P <0.001	-3.2 (-5.8- -0.6) P = 0.017	-6.1 (-9.5- -2.7) P <0.001	0.003	0.001	0.2	0.1
PAD	-4.6 (-6.3- -3.0) P <0.001	-1.2 (-2.6- 0.3) P = 0.1	-4.4 (-6.3- -2.5) P <0.001	0.011	0.018	0.013	0.6
mPAP	-7.9 (-9.4- -6.3) P <0.001	-0.9 (-2.6- 0.7) P = 0.3	-4.8 (-6.7- -2.9) P <0.001	<0.001	<0.001	0.024	0.4
PCWP	-7.5 (-9.0- -6.0) P <0.001	-2.5 (-3.5- -1.4) P<0.001	-4.3 (-6.4- -2.2) P <0.001	<0.001	<0.001	0.3	0.006
TPG	1.0 (-0.7- 2.7) P = 0.3	1.8 (-0.02- 3.7) P = 0.052	-1.6 (-3.8- 0.7) P = 0.2	0.3	0.6	0.1	0.3
DPG	3.6 (1.9-5.3) P <0.001	2.6 (0.9-4.4) P = 0.003	-0.5 (-3.0- 2.0) P = 0.7	0.08	0.5	0.06	0.01
CO	-0.4 (-0.8- -0.1) P = 0.005	-0.3 (-0.5- -0.02) P = 0.031	0.4 (-0.1- 1.0) P = 0.1	0.007	0.4	0.009	0.002
CI	-0.2 (-0.3- -0.07) P = 0.003	-0.1 (-0.2- 0.04) P = 0.2	0.2 (-0.1- 0.5) P = 0.1	0.012	0.2	0.022	0.003
TPR (natural log)	-0.1 (-0.2- -0.05) P = 0.001	-0.02 (-0.1- 0.03) P = 0.4	-0.2 (-0.3- -0.1) P <0.001	0.004	0.049	0.002	0.2
PVR (natural log)	0.2 (0.03- 0.3) P = 0.015	0.1 (0.04- 0.2) P = 0.002	-0.1 (-0.2- -0.002) P = 0.047	0.007	0.4	0.010	0.002
HR	0.4 (-1.3- 2.0)	-0.6 (-3.0- 1.8)	-2.2 (-5.3- 0.8)	0.7	>0.9	0.4	0.5

	P = 0.7	P = 0.6	P = 0.1				
C pa	0.97 (0.25-1.68) P = 0.008	0.11 (-0.05-0.26) P = 0.2	0.39 (0.11-0.67) P = 0.006	0.006	0.003	0.072	0.5
SBP	-6.4 (-12.1- -0.8) P = 0.025	-7.5 (-10.9- -4.0) P <0.001	-10.9 (-16.7- -5.2) P <0.001	0.5	0.5	0.5	0.3
DBP	-3.2 (-6.5- 0.1) P = 0.06	-3.8 (-6.0- -1.7) P <0.001	-5.2 (-8.4- -2.1) P = 0.001	0.6	0.4	0.9	0.4
Mean BP	-5.4 (-9.6- -1.1) P = 0.013	-5.1 (-7.6- -2.6) P<0.001	-7.5 (-11.0- -4.0) P <0.001	0.6	0.9	0.4	0.4
C sys	0.01 (-0.09-0.11) P = 0.9	0.05 (-0.12-0.21) P = 0.6	0.35 (0.13-0.58) P = 0.002	0.089	0.080	0.061	0.031
SVR (natural log)	0.10 (0.03- 0.18) P = 0.008	-0.01 (-0.07-0.05) P = 0.8	-0.15 (-0.25- -0.05) P = 0.004	0.002	0.036	0.028	<0.001
PVR/SVR (square root)	0.02 (-0.01-0.05) P = 0.2	0.03 (0.01- 0.05) P = 0.008	0.01 (-0.02-0.04) P = 0.4	0.4	0.2	0.4	0.8
O2 sat	-0.7 (-1.5- 0.1) P = 0.1	-0.3 (-1.1- 0.5) P = 0.4	-0.2 (-1.7- 1.3) P = 0.8	0.7	0.4	>0.9	0.6
Meth. Hgb (square root)	0.16 (0.06- 0.26) P = 0.003	0.29 (0.19- 0.38) P <0.001	0.18 (0.05-0.32) P = 0.007	0.2	0.07	0.3	0.7

Table E3. Effect of each dose of intervention on study variables. Each cell indicates the β (mean change of variable, and 95% CI) during the intervention compared to the baseline measure from mixed effect model. Note: Right ventricular (RV) pressure was not assessed at the 45 mg dose to minimize manipulation of the pulmonary artery catheter as per protocol. Variables requiring transformation are noted.

	Dose	**PH-HFpEF**	**Group 1 PAH**	**Group 3 PH**
RA (square root)	45	-0.95 (-1.16- -0.74)	-0.29 (-0.52- -0.05)	-0.56 (-0.96- -0.15)
	90	-1.22 (-1.44- -1.00)	-0.64 (-0.87- -0.40)	-0.83 (-1.25- -0.41)
	P for trend	<0.001	<0.001	<0.001
RVS	45	NA	-1.3 (-8.6- 5.9)	-1.9 (-6.8- 3.0)
	90	-10.4 (-13.1- -7.7)	-2.1 (-6.9- 2.7)	-4.8 (-8.3- -1.2)
	P for trend	NA	0.4	0.003
RVD	45	NA	-1.3 (-4.0- 1.4)	3.7 (-1.4- 8.8)
	90	-6.8 (-9.6- -4.0)	-2.3 (-4.1- -0.6)	-4.5 (-8.3- -0.7)
	P for trend	NA	0.007	0.015
PAS	45	-9.6 (-12.1- -7.1)	-4.1 (-6.8- -1.4)	-6.2 (-9.8- -2.6)
	90	-10.2 (-12.9- -7.6)	-2.2 (-4.9- 0.4)	-6.0 (-9.7- -2.6)
	P for trend	<0.001	0.9	0.026
PAD	45	-4.2 (-5.9- -2.5)	-0.9 (-2.4- 0.6)	-3.8 (-5.8- -1.9)
	90	-5.3 (-7.1-3.6)	-1.4 (-2.9- 0.1)	-5.1 (-7.0- -3.1)
	P for trend	<0.001	0.1	<0.001
mPAP	45	-7.6 (-9.3- -6.0)	-1.0 (-2.7- 0.8)	-4.4 (-6.4- -2.4)
	90	-8.2 (-9.9- -6.5)	-0.9 (-2.6- 0.9)	-5.3 (-7.4- -3.3)
	P for trend	<0.001	0.5	<0.001
PCWP	45	-6.9 (-8.4- -5.4)	-2.0 (-3.0- -0.9)	-3.1 (-5.0- -1.2)
	90	-8.4 (-9.9- -6.8)	-2.9 (-4.0- -1.9)	-5.7 (-7.7- -3.8)
	P for trend	<0.001	<0.001	<0.001
TPG	45	0.5 (-1.2- 2.3)	1.3 (-0.6- 3.2)	-1.8 (-3.8- 0.4)
	90	1.7 (-0.2- 3.5)	2.3 (0.4- 4.2)	0.0 (-2.2- 2.3)
	P for trend	0.033	0.008	0.4
DPG	45	3.4 (1.7-5.2)	2.5 (0.7-4.3)	-1.4 (-3.9- 1.1)
	90	3.9 (2.0-5.7)	2.8 (0.9-4.6)	0.8 (-1.8- 3.3)
	P for trend	0.001	0.018	0.18
CO	45	-0.3 (-0.6- -0.02)	-0.2 (-0.5- -0.01)	0.1 (-0.2- 0.4)
	90	-0.6 (-0.9- -0.3)	-0.3 (-0.5- -0.01)	0.4 (0.1- 0.7)
	P for trend	<0.001	0.1	0.002
CI	45	-0.2 (-0.3- 0.02)	-0.1 (-0.2- 0.1)	0.1 (-0.2- 0.4)
	90	-0.3 (-0.4- -0.1)	-0.1 (-0.2- 0.04)	0.4 (0.1- 0.7)
	P for trend	<0.001	0.3	0.002
TPR	45	-0.1 (-0.2- -0.1)	-0.02 (-0.1- 0.04)	-0.2 (-0.2- -0.1)
	90	-0.1 (-0.2- -0.02)	-0.03 (-0.1- 0.03)	-0.3 (-0.3- -0.2)
	P for trend	0.2	0.3	<0.001
PVR	45	0.1 (-0.01- 0.3)	0.09 (0.02- 0.2)	-0.1 (-0.2- 0.003)
	90	0.2 (0.09- 0.4)	0.1 (0.05- 0.2)	-0.1 (-0.2- 0.01)
	P for trend	0.001	0.002	0.2
HR	45	0.3 (-1.4- 2.1)	-0.8 (-3.4- 1.7)	-2.3 (-5.5- 0.9)
	90	0.4 (-1.4- 2.2)	-0.3 (-2.9- 2.2)	-2.2 (-5.4- 1.1)
	P for trend	0.7	0.9	0.4
C pa	45	1.19 (0.37-1.86)	0.17 (0.002-0.33)	0.36 (0.07-0.66)

	90	0.75 (-0.02-1.53)	0.05 (-0.11-0.21)	0.43 (0.13-0.74)
	P for trend	0.06	0.6	0.006
SBP	45	-4.6 (-10.3- 1.1)	-6.8 (-10.3- -3.2)	-10.0 (-16.1- -4.3)
	90	-9.1 (-15.1- -3.1)	-8.2 (-11.8- -4.6)	-12.8 (-12.2- -18.4)
	P for trend	0.001	<0.001	0.001
DBP	45	-1.9 (-5.2-1.4)	-3.3 (-5.5- -1.1)	-5.2 (-8.6- -1.9)
	90	-5.1 (-8.6- -1.7)	-4.4 (-6.6- -2.2)	-5.2 (-8.7- -1.8)
	P for trend	0.001	<0.001	0.027
Mean BP	45	-3.8 (-8.1- 0.5)	-4.6 (-7.2- -2.0)	-7.2 (-10.9- -3.5)
	90	-7.6 (-12.1- -3.1)	-5.6 (-8.2- -3.0)	-7.9 (-11.7- -4.1)
	P for trend	<0.001	<0.001	0.002
C sys	45	0.01 (-0.10- 0.11)	0.05 (-0.12-0.23)	0.27 (0.04-0.50)
	90	0.01 (-0.10- 0.12)	0.04 (-0.14-0.22)	0.47 (0.23-0.70)
	P for trend	0.9	0.7	<0.001
SVR (natural log)	45	0.08 (0.01- 0.16)	-0.01 (-0.08- 0.05)	-0.12 (-0.22- -0.02)
	90	0.13 (0.05- 0.21)	0.0 (-0.07- 0.06)	-0.19 (-0.30- -0.09)
	P for trend	0.002	0.9	<0.001
PVR/SVR (square root)	45	0.01 (-0.02- 0.04)	0.02 (-0.002- 0.04)	0.003 (-0.03- 0.03)
	90	0.03 (0.001- 0.06)	0.04 (0.02- 0.06)	0.02 (-0.01- 0.05)
	P for trend	0.013	<0.001	0.2
O2 sat	45	-0.6 (-1.4- 0.3)	-0.4 (-1.2- 0.5)	-0.5 (-2.1- 1.0)
	90	-0.8 (-1.7- 0.1)	-0.2 (-1.1- 0.6)	0.2 (-1.3- 1.8)
	P for trend	0.07	0.8	0.4
Meth. Hgb (square root)	45	0.06 (-0.01- 0.13)	0.17 (0.09- 0.23)	0.11 (-0.001- 0.23)
	90	0.30 (0.22- 0.37)	0.41 (0.38- 0.49)	0.29 (0.17- 0.41)
	P for trend	<0.001	<0.001	<0.001

Table E4. Effect of inhaled nitric oxide (iNO) on study variables. Each cell indicates the β (mean change of variable, and 95% CI) during the intervention compared to the baseline measure from mixed effect model. Note: Right ventricular (RV) pressure was not assessed at the 45 mg dose to minimize manipulation of the pulmonary artery catheter as per protocol. The first P value indicates the effect of iNO vs baseline, noted as (iNO); the second P value indicates the difference between the effects of iNO and nitrite in each group. Variables requiring transformation are noted.

	PH-HFpEF	**Group 1 PAH**	**Group 3 PH**	P value for interaction of groups	P value for PH-HFpEF vs Group 1	P value for Group 3 vs 1	P value for PH-HFpEF vs Group 3
RA (square root)	-0.25 (-0.42- -0.09) P = 0.002 (iNO)	-0.20 (-0.45-0.05) P = 0.1 (iNO)	-0.58 (-1.16- -0.01) P = 0.047 (iNO)	0.4	0.6	0.3	0.2
	P <0.001	P < 0.001	P = 0.7	--	--	--	--
RVS	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	--	--	--	--
RVD	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	--	--	--	--
PAS	-7.3 (-11.4- -3.2) P <0.001 (iNO)	-10.9 (-14.9- -6.9) P <0.001 (iNO)	-12.2 (-18.7- -5.6) P < 0.001 (iNO)	0.4	0.3	0.7	0.3
	P = 0.12	P <0.001	P = 0.033	--	--	--	--
PAD	-2.4 (-4.6- -0.2) P = 0.033 (iNO)	-2.4 (-4.3- -0.4) P = 0.020 (iNO)	-3.0 (-8.6- 2.6) P = 0.3 (iNO)	>0.9	>0.9	0.8	>0.9
	P = 0.002	P = 0.1	P = 0.6	--	--	--	--
mPAP	-4.3 (-6.7- -1.9) P <0.001 (iNO)	-5.2 (-7.4- -3.0) P <0.001 (iNO)	-6.1 (-10.9- -1.3) P = 0.013 (iNO)	0.8	0.6	0.7	0.6
	P < 0.001	P < 0.001	P = 0.6	--	--	--	--
PCWP	0.60 (-1.69-2.89) P = 0.6 (iNO)	0.84 (-0.42-2.10) P = 0.2 (iNO)	-1.14 (-2.94-0.66) P = 0.2 (iNO)	0.4	0.8	0.2	0.6
	P < 0.001	P < 0.001	P < 0.001	--	--	--	--
TPG	-4.9 (-7.6- -2.2) P <0.001 (iNO)	-6.5 (-9.0- -3.9) P <0.001 (iNO)	-6.6 (-12.5- -0.8) P = 0.027 (iNO)	0.7	0.5	>0.9	0.5
	P < 0.001	P < 0.001	P = 0.043	--	--	--	--

DPG	-3.0 (-5.6- -0.5) P = 0.02	-3.4 (-5.5- -1.2) P = 0.002	-4.2 (-9.3- 1.0) P = 0.11	0.9	0.8	0.7	0.7
	P < 0.001	P < 0.001	P = 0.3	--	--	--	--
CO	-0.16 (-0.66-0.33) P = 0.5 (iNO)	-0.02 (-0.27-0.23) P = 0.9 (iNO)	-0.26 (-0.63-0.11) P = 0.2 (iNO)	0.6	0.5	0.4	0.5
	P = 0.1	P < 0.001	P < 0.001	--	--	--	--
CI	-0.08 (-0.30-0.14) P = 0.5 (iNO)	0.01 (-0.13-0.14) P = 0.9 (iNO)	-0.12 (-0.31-0.06) P = 0.2 (iNO)	0.6	0.5	0.4	0.5
	P = 0.1	P = 0.002	P < 0.001	--	--	--	--
TPR (natural log)	-0.08 (-0.20-0.03) P = 0.1 (iNO)	-0.13 (-0.21- -0.06) P <0.001 (iNO)	-0.14 (-0.31-0.03) P = 0.1 (iNO)	0.8	0.5	0.9	0.5
	P = 0.5	P < 0.001	P = 0.4	--	--	--	--
PVR (natural log)	-0.46 (-0.82- -0.11) P = 0.011 (iNO)	-0.23 (-0.35- -0.12) P <0.001 (iNO)	-0.24 (-0.52-0.03) P = 0.08 (iNO)	0.3	0.1	0.9	0.1
	P < 0.001	P < 0.001	P = 0.3	--	--	--	--
HR	-3 (-4- -1) P = 0.005 (iNO)	-4 (-7- -2) P = 0.002 (iNO)	-0.5 (-2- 1) P = 0.5 (iNO)	0.2	0.3	0.09	0.3
	P < 0.001	P < 0.001	0.2	--	--	--	--
C pa	0.59 (-0.09-1.26) P = 0.09 (iNO)	0.54 (0.31-0.77) P <0.001 (iNO)	0.46 (-0.15-1.08) P = 0.1 (iNO)	0.9	0.8	0.8	0.3
	P = 0.001	P < 0.001	0.8	--	--	--	--
SBP	0.0 (-5.26- 5.26) P > 0.9 (iNO)	0.45 (-01.74-2.64) P = 0.7 (iNO)	1.17 (-4.48-6.81) P = 0.7 (iNO)	0.9	0.9	0.8	0.9
	P < 0.001	P < 0.001	P < 0.001	--	--	--	--
DBP	-2.8 (-7.05-1.45) P = 0.2 (iNO)	-0.85 (-2.41-0.70) P = 0.3 (iNO)	-2.00 (-4.37-0.37) P = 0.1 (iNO)	0.5	0.3	0.6	0.3
	P = 0.8	P < 0.001	P = 0.001	--	--	--	--
Mean BP	-2.37 (-6.75-2.01)	-0.41 (-1.86-1.05)	-0.66 (-3.73-2.42)	0.6	0.3	0.9	0.3

	P = 0.3 (iNO)	P = 0.6 (iNO)	P = 0.7 (iNO)				
	P < 0.001	P < 0.001	P <0.001	--	--	--	--
C sys	0.01 (-0.20-0.22) P = 0.9 (iNO)	0.03 (-0.12-0.17) P = 0.7 (iNO)	-0.11 (-0.29-0.07) P = 0.2 (iNO)	0.6	0.9	0.3	0.9
	P > 0.9	P = 0.9	P < 0.0001	--	--	--	--
SVR (natural log)	0.02 (-0.10-0.13) P = 0.8 (iNO)	0.01 (-0.05-0.07) P = 0.8 (iNO)	0.08 (0.01-0.16) P = 0.035 (iNO)	0.5	0.9	0.3	0.9
	P = 0.050	P < 0.001	P < 0.001	--	--	--	--
PVR/SVR (square root)	-0.08 (-0.14- -0.02) P = 0.007 (iNO)	-0.07 (-0.10- -0.05) P < 0.001 (iNO)	-0.09 (-0.17-0.01) P = 0.021 (iNO)	0.9	0.8	0.6	0.8
	P < 0.001	P < 0.001	P = 0.005	--	--	--	--
O2 sat	4 (2- 5) P < 0.001 (iNO)	3 (2- 4) P < 0.001 (iNO)	3 (1- 6) P = 0.006 (iNO)	0.7	0.7	0.9	0.9
	P < 0.001	P < 0.001	P < 0.001	--	--	--	--