SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Search strategy

1. Component 'right ventricle'

"right ventricle"[tiab] OR "right ventricles"[tiab] OR "right ventricular"[tiab] OR "ventriculus dexter"[tiab] OR "right heart"[tiab] OR "RV"[tiab]

2. Component 'pressure load'

"pressure load"[tiab] OR " pressure loading"[tiab] OR " pressure loaded"[tiab] OR " pressure loads"[tiab] OR " pressure overload"[tiab] OR " pressure overloading"[tiab] OR " pressure overloaded"[tiab] OR "pressure overloads"[tiab] OR "increased afterload"[tiab] OR "increased afterloading"[tiab] OR "afterloaded"[tiab] OR "increased afterloads"[tiab] OR "pulmonary artery banding"[tiab] OR " pulmonary hypertension"[tiab] OR "pulmonary arterial hypertension"[tiab] OR "pulmonary valve stenosis"[tiab] OR "pulmonary valve calcification"[tiab] OR "calcification pulmonary valve"[tiab] OR "pulmonary valve diseases"[tiab] OR "pulmonary valve disease"[tiab] OR "pulmonary stenosis"[tiab] OR "stenosis pulmonary valve"[tiab] OR "pulmonary outflow tract obstruction"[tiab] OR "obstruction pulmonary outflow tract"[tiab] OR "pulmonary artery obstruction"[tiab] OR "pulmonary artery stenosis"[tiab]

3. Component 'metabolism'

"metabolism"[tiab] OR "metabolic"[tiab] OR "energy metabolism"[tiab] OR "basal metabolism"[tiab] OR "carbohydrate metabolism"[tiab] OR "metabolic network"[tiab] OR "metabolic pathways"[tiab] OR "metabolic networks and pathways"[tiab] OR "biosynthetic pathways"[tiab] OR "metabolic activation"[tiab] OR "metabolic inactivation"[tiab] OR "secondary metabolism"[tiab] OR "metabolic remodeling"[tiab] OR "metabolic remodelling"[tiab] OR "metabolic"[tiab] OR "metabolic reprogramming"[tiab] OR "metabolite"[tiab] OR "metabolomic"[tiab] OR "metabolomics"[tiab] OR "metabolite profile"[tiab] OR "metabolites profiles"[tiab] OR "metabolite derangements"[tiab] OR "metabolomic signatures"[tiab] OR "substrate flux"[tiab] OR "mitochondria"[tiab] OR "mitochondrial"[tiab] OR "mitochondrion"[tiab] OR "mitochondrial energy transduction"[tiab] OR "glucose metabolism"[tiab] OR " glucose oxidation"[tiab] OR "gluconeogenesis"[tiab] OR "glycogenolysis"[tiab] OR "glycolysis"[tiab] OR "glycosylation"[tiab] OR "pyruvate"[tiab] OR "glucose"[tiab] OR "pentose phosphate pathway"[tiab] OR "fatty acid"[tiab] OR "fatty acids"[tiab] OR "long chain fatty acids"[tiab] OR "lipid metabolism"[tiab] OR "lipolysis"[tiab] OR "lipoylation"[tiab] OR "fatty acid oxidation"[tiab] OR "lipotoxicity"[tiab] OR "triglyceride"[tiab] OR "ceramide"[tiab] OR "lipid deposition"[tiab] OR "beta-oxidation"[tiab] OR "beta oxidation"[tiab] OR "fatty acid transport"[tiab] OR "β-oxidation"[tiab] OR "branched chain amino acids"[tiab] OR "branched chain amino acid"[tiab] OR "amino acid"[tiab] OR "amino acids"[tiab] OR "BCAA"[tiab] OR "branched chain aminotransferase"[tiab] OR "branched-chain aminotransferase"[tiab] OR "BCAT"[tiab] OR "brached chain keto acids"[tiab] OR "brached-chain keto acids"[tiab] OR "BCKA"[tiab] OR "BCKA dehydrogenase complex"[tiab] OR "BCKD"[tiab] OR "ketone"[tiab] OR "ketones"[tiab] OR "ketogenesis"[tiab] OR "ketosis"[tiab] OR "ketone body"[tiab] OR "citric acid cycle"[tiab] OR "tricarboxylic acid cycle"[tiab] OR "TCA cycle"[tiab] OR "Krebs cycle"[tiab] OR "ATP"[tiab] OR "ADP"[tiab] OR "adenosine diphosphate"[tiab] OR "adenosine triphosphate"[tiab] OR "respiratory transport"[tiab] OR "oxidation-reducation"[tiab] OR "oxidative phosphorylation"[tiab] OR "phosphorylation"[tiab] OR "electron transport"[tiab] OR "electron transport chain"[tiab] OR "metabolic targets"[tiab] OR "metabolic therapy"[tiab] OR "fatty acid oxidation inhibitor"[tiab] OR "glucose oxidation inhibitor"[tiab] OR "fatty acid uptake inhibitor"[tiab] OR "metabolic inhibitor"[tiab] OR "metabolic activator"[tiab] OR "inhibition of metabolic pathways"[tiab] OR "inhibition of metabolic pathway”[tiab] OR “metabolic inducers”[tiab] OR “metabolic inducer”[tiab] OR “metabolic inducement”[tiab] OR “metabolic activation”[tiab] OR “metabolic regulation”[tiab] OR “regulation of metabolism”[tiab] OR “regulation of fatty acid”[tiab] OR “regulation of fatty acids”[tiab] OR “stimulation of fatty acid metabolism”[tiab] OR “inhibition of fatty acid metabolism”[tiab] OR “regulation of glucose oxidation”[tiab] OR “regulation of glycolysis”[tiab] OR “stimulation of glucose oxidation”[tiab] OR “inhibition of glycolysis”[tiab] OR “inhibition of glucose oxidation”[tiab] OR “amino acid administration”[tiab] OR “amino acids administration”[tiab] OR “metabolic defect”[tiab] OR “catabolic defect”[tiab] OR “cell respiration”[tiab] OR “cell hypoxia”[tiab] OR “respiratory burst”[tiab] OR “anaerobiosis”[tiab] OR “oxidative stress”[tiab]

Table S1. List of studies studying metabolic parameters in the pressure loaded right ventricle included for full text review.

Author	Year	Title	PMID	Embase Accession ID	Animal	Human	Specie	Model	Disease	Inclusion meta-analysis
Cooper, et al.[1]	1974	Normal myocardial function and energetics after reversing pressure overload hypertrophy	4274811	1975096311	x		cat	PAB		
Cooper, et al.[2]	1981	Chronic progressive pressure overload of the cat right ventricle.	6450649		x		cat	PAB		
Reibel, et al.[3]	1983	Altered coenzyme A and carnitine metabolism in pressure-overload hypertrophied hearts.	6222659		x		cat			
Lauva, et al.[4]	1986	Control of myocardial tissue components and cardiocyte organelles in pressure-overload hypertrophy of the cat right ventricle.	2877565		x		cat	PAB		x
Schneider, et al.[5]	1987	Development and regression of right heart ventricular hypertrophy: biochemical and morphological aspects.	2963447		x					
Olivetti, et al.[6]	1988	Cellular basis of wall remodeling in long-term pressure overload-induced right ventricular hypertrophy in rats.	2970334		x		rat	PAB		x
Hung, et al.[7]	1988	Morphometry of right ventricular papillary muscle in rat during development and regression of hypoxia-induced hypertension.	3381706		x					
Saito, et al.[8]	1991	Oxygen metabolism of the hypertrophic right ventricle in open chest dogs.	1839241		x		dog	PAB		
Morioka, et al.[9]	1992	Changes in contractile and non-contractile proteins, intracellular Ca2+ and ultrastructures during the development of right ventricular hypertrophy and failure	1534855		x		rat	MCT60		

		in rats.							
Sivitz, et al.[10]	1992	Pretranslational regulation of two cardiac glucose transporters in rats exposed to hypobaric hypoxia.	1415537	x		rat	hypoxia		x
Baudet, et al.[11]	1994	Biochemical, mechanical and energetic characterization of right ventricular hypertrophy in the ferret heart.	7731052	x		ferret	PAC		
Ishikawa, et al.[12]	1995	Enalapril improves heart failure induced by monocrotaline without reducing pulmonary hypertension in rats: roles of preserved myocardial creatine kinase and lactate dehydrogenase isoenzymes.	7721499	x		rat	MCT50		
Do, et al.[13]	1995	Intracellular pH during hypoxia in normal and hypertrophied right ventricle of ferret heart.	7602610	x		ferret	PAB		
Sack, et al.[14]	1997	A role for Sp and nuclear receptor transcription factors in a cardiac hypertrophic growth program.	9177236	x		mouse	PAB		x
Nagaya, et al.[15]	1998	Impaired regional fatty acid uptake and systolic dysfunction in hypertrophied right ventricle.	9776267		x			PH (mPAP > 20)	
Rumsey, et al.[16]	1999	Adaptation to hypoxia alters energy metabolism in rat heart.	9887019	x		rat	hypoxia		x
O'Brien, et al.[17]	1999	F1-ATP synthase beta-subunit and cytochrome c transcriptional regulation in right ventricular hemodynamic overload and hypertrophically stimulated cardiocytes.	10072725	x		feline (cat)	PAB		
Matsushita, et al.[18]	2000	Use of [123I]-BMIPP myocardial scintigraphy for the clinical evaluation of a fatty-acid metabolism disorder of the right ventricle in chronic respiratory and pulmonary vascular disease.	10983861		x			RVPO	
Bitar, et al.[19]	2002	Modulation of ceramide content and lack of apoptosis in the chronically hypoxic neonatal rat heart.	11809907	x		rat	hypoxia		

Ecarnot-Laubreit, et al.[20]	2003	The activation pattern of the antioxidant enzymes in the right ventricle of rat in response to pressure overload is of heart failure type.	14503927	x		rat	MCT60		
Farahmand, et al.[21]	2004	Antioxidant and oxidative stress changes in experimental cor pulmonale.	15228082	x		rat	MCT60		
Cisar, et al.[22]	2004	Differential expression of mitochondrial electron transport chain proteins in cardiac tissues of broilers from pulmonary hypertension syndrome-resistant and -susceptible lines.	15339019	x		broiler	hypoxia		
Sharma, et al.[23]	2004	Dynamic changes of gene expression in hypoxia-induced right ventricular hypertrophy.	14630626	x		rat	hypoxia		x
Nouette-Gaulain, et al.[24]	2004	Time course of differential mitochondrial energy metabolism adaptation to chronic hypoxia in right and left ventricles.	15769456	x		rat	hypoxia		x
Adrogue, et al.[25]	2005	Acclimatization to chronic hypobaric hypoxia is associated with a differential transcriptional profile between the right and left ventricle.	16180091	x		rat	hypoxia		x
van Beek-Harmsen and van der Laarse[26]	2005	Immunohistochemical determination of cytosolic cytochrome C concentration in cardiomyocytes.	15995138	x		rat	MCT40		
Schott, et al.[27]	2005	Pressure overload and neurohumoral activation differentially affect the myocardial proteome.	15732135	x		rat	MCT50		
Faber, et al.[28]	2005	Proteomic changes in the pressure overloaded right ventricle after 6 weeks in young rats: correlations with the degree of hypertrophy.	15912512	x		rat	PAB		
Kluge, et al.[29]	2005	Different mechanisms for changes in glucose uptake of the right and left ventricular myocardium in pulmonary hypertension.	15632029		x			PH	

Oikawa, et al.[30]	2005	Increased [18F]fluorodeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and the effect of epoprostenol.	15936618		x			PH	
Redout, et al.[31]	2007	Right-ventricular failure is associated with increased mitochondrial complex II activity and production of reactive oxygen species.	17582388	x		rat	MCT80		
Faber, et al.[32]	2007	Time dependent changes in cytoplasmic proteins of the right ventricle during prolonged pressure overload.	17603072	x		rat	PAB		
Basu, et al.[33]	2007	Etiopathologies associated with intercostal muscle hypermetabolism and prominent right ventricle visualization on 2-deoxy-2[F-18]fluoro-D-glucose-positron emission tomography: significance of an incidental finding and in the setting of a known pulmonary disease.	17610018		x			Varied diseases	
Nagendran, et al.[34]	2008	A dynamic and chamber-specific mitochondrial remodeling in right ventricular hypertrophy can be therapeutically targeted.	18603070	x		rat	MCT		
Broderick and King.[35]	2008	Upregulation of GLUT-4 in right ventricle of rats with monocrotaline-induced pulmonary hypertension.	19043358	x		rat	MCT60		x
Mouchaers, et al.[36]	2009	Endothelin receptor blockade combined with phosphodiesterase-5 inhibition increases right ventricular mitochondrial capacity in pulmonary arterial hypertension.	19395550	x		rat	MCT40		
Sheikh, et al.[37]	2009	Right ventricular hypertrophy with early dysfunction: A proteomics study in a neonatal model.	19379982	x		piglet	PAB		x
Redout, et al.[38]	2010	Antioxidant treatment attenuates pulmonary arterial hypertension-induced heart failure.	20061549	x		rat	MCT80		

Yen, et al.[39]	2010	Sildenafil limits monocrotaline-induced pulmonary hypertension in rats through suppression of pulmonary vascular remodeling.	20224427	x		rat	MCT60		
Piao, et al.[40]	2010	The inhibition of pyruvate dehydrogenase kinase improves impaired cardiac function and electrical remodeling in two models of right ventricular hypertrophy: resuscitating the hibernating right ventricle.	19949938	x		rat	MCT60 & PAB		x
Drake, et al.[41]	2011	Molecular signature of a right heart failure program in chronic severe pulmonary hypertension.	21719795	x		rat	PAB + Suhx +Cu2diet		
Saini-Chohan, et al.[42]	2011	Persistent pulmonary hypertension results in reduced tetralinoleoyl-cardiolipin and mitochondrial complex II + III during the development of right ventricular hypertrophy in the neonatal pig heart.	21841017	x		piglet	hypoxia		
Baandrup, et al.[43]	2011	Pressure load: the main factor for altered gene expression in right ventricular hypertrophy in chronic hypoxic rats.	21246034	x		rat	hypoxia + PAB		
Bokhari, et al.[44]	2011	PET imaging may provide a novel biomarker and understanding of right ventricular dysfunction in patients with idiopathic pulmonary arterial hypertension.	21926260		x			iPAH	
Wong, et al.[45]	2011	Right ventricular failure in idiopathic pulmonary arterial hypertension is associated with inefficient myocardial oxygen utilization.	21900188		x			iPAH	
Wong, et al.[46]	2011	Systolic pulmonary artery pressure and heart rate are main determinants of oxygen consumption in the right ventricular myocardium of patients with idiopathic pulmonary arterial hypertension.	22016028		x			iPAH	

Qipshidze, et al.[47]	2012	Autophagy mechanism of right ventricular remodeling in murine model of pulmonary artery constriction.	22101525		x		mouse	PAB		
Mosele, et al.[48]	2012	Effects of purple grape juice in the redox-sensitive modulation of right ventricular remodeling in a pulmonary arterial hypertension model.	22441302		x		rat	MCT60		
Khoo, et al.[49]	2012	Obesity-induced tissue free radical generation: an in vivo immuno-spin trapping study.	22564528		x		mouse	Diet + DMPO + MCT60		
Fang, et al.[50]	2012	Therapeutic inhibition of fatty acid oxidation in right ventricular hypertrophy: exploiting Randle's cycle.	21874543		x		rat	PAB		x
Fang, et al.[51]	2012	Comparison of 18F-FDG uptake by right ventricular myocardium in idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease.	23130105			x			iPAH vs. CHD-PAH	
Wong, et al.[52]	2013	11C-Acetate clearance as an index of oxygen consumption of the right myocardium in idiopathic pulmonary arterial hypertension: a validation study using 15O-labeled tracers and PET.	23735834			x			iPAH	
Sutendra, et al.[53]	2013	A metabolic remodeling in right ventricular hypertrophy is associated with decreased angiogenesis and a transition from a compensated to a decompensated state in pulmonary hypertension.	23846254		x		rat	MCT		x
Piao, et al.[54]	2013	Cardiac glutaminolysis: a maladaptive cancer metabolism pathway in the right ventricle in pulmonary hypertension.	23794090		x		rat	PAB & MCT60		x
Drake, et al.[55]	2013	Chronic carvedilol treatment partially reverses the right ventricular failure transcriptional profile in experimental pulmonary hypertension.	23632417	2013387359	x		rat	SuHx		
Alzoubi, et al.[56]	2013	Dehydroepiandrosterone restores right ventricular structure and function in rats	23585128		x		rat	SuHx		

		with severe pulmonary arterial hypertension.								
Piao, et al.[57]	2013	FOXO1-mediated upregulation of pyruvate dehydrogenase kinase-4 (PDK4) decreases glucose oxidation and impairs right ventricular function in pulmonary hypertension: therapeutic benefits of dichloroacetate.	23247844		x	x	rat	FHR	PAH	x
Gomez-Arroyo, et al.[58]	2013	Metabolic gene remodeling and mitochondrial dysfunction in failing right ventricular hypertrophy secondary to pulmonary arterial hypertension.	23152488		x	x	rat	SuHx & PAB	PAH	x
Friehs, et al.[59]	2013	Pressure-overload hypertrophy of the developing heart reveals activation of divergent gene and protein pathways in the left and right ventricular myocardium.	23262132		x		rabit	PAB		
Enache, et al.[60]	2013	Skeletal muscle mitochondrial dysfunction precedes right ventricular impairment in experimental pulmonary hypertension.	23099843		x		rat	MCT60		x
Kojonazarov, et al.[61]	2013	The peroxisome proliferator-activated receptor Î²/Î´ agonist GW0742 has direct protective effects on right heart hypertrophy.	25006409		x		mice	PAB		
Yoshinaga, et al.[62]	2013	Attenuated right ventricular energetics evaluated using Â¹Â¹C-acetate PET in patients with pulmonary hypertension.	24615469			x			PH	
Wang, et al.[63]	2013	Evaluation of right ventricular volume and ejection fraction by gated (18)F-FDG PET in patients with pulmonary hypertension: comparison with cardiac MRI and CT.	23354658			x			PH	
Lundgrin, et al.[64]	2013	Fasting 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography to detect metabolic changes in pulmonary arterial hypertension hearts over 1 year.	23509326			x			PAH	
Ikeda, et al.[65]	2014	Crucial role of rho-kinase in pressure overload-induced right ventricular hypertrophy and dysfunction in mice.	24675663	2014358537	x		mouse	PAB		

Hemnes, et al.[66]	2014	Evidence for right ventricular lipotoxicity in heritable pulmonary arterial hypertension.	24274756	x		mouse	BMPR2 & PAB		
Rawat, et al.[67]	2014	Increased reactive oxygen species, metabolic maladaptation, and autophagy contribute to pulmonary arterial hypertension-induced ventricular hypertrophy and diastolic heart failure.	25267798	x		rat	SuHx		
Liu, et al.[68]	2014	Inhibition of NOX/VPO1 pathway and inflammatory reaction by trimethoxystilbene in prevention of cardiovascular remodeling in hypoxia-induced pulmonary hypertensive rats.	24492474	x		rat	hypoxia		
Ahmed, et al.[69]	2014	Naringenin adds to the protective effect of L-arginine in monocrotaline-induced pulmonary hypertension in rats: favorable modulation of oxidative stress, inflammation and nitric oxide.	24878387	x		rat	MCT60		
Frazziano, et al.[70]	2014	Nox-derived ROS are acutely activated in pressure overload pulmonary hypertension: indications for a seminal role for mitochondrial Nox4.	24213612	x		mouse	PAC + Nox2-/-, p47phox-/-		
Nergui, et al.[71]	2014	Role of endothelial nitric oxide synthase and collagen metabolism in right ventricular remodeling due to pulmonary hypertension.	24705390	x		mice	hypoxia + eNOS-/-		
Ahmed, et al.[72]	2014	Role of oxidative stress, inflammation, nitric oxide and transforming growth factor-beta in the protective effect of diosgenin in monocrotaline-induced pulmonary hypertension in rats.	25062790	x		rat	MCT60		
Zhang, et al.[73]	2014	Up-regulation of hexokinase1 in the right ventricle of monocrotaline induced pulmonary hypertension.	25287584	x		rat	MCT50		x
Tatebe, et al.[74]	2014	Enhanced [18F]fluorodeoxyglucose accumulation in the right ventricular free wall predicts long-term prognosis of	24408936		x			PAH	

		patients with pulmonary hypertension: a preliminary observational study.								
Yang, et al.[75]	2014	The ratio of (18)F-FDG activity uptake between the right and left ventricle in patients with pulmonary hypertension correlates with the right ventricular function.	24662662			x			PH	
Paulin, et al.[76]	2015	A miR-208-Mef2 axis drives the decompensation of right ventricular function in pulmonary hypertension.	25287062		x		rat	MCT		x
Moreira-Goncalyes, et al. [77]	2015	Cardioprotective effects of early and late aerobic exercise training in experimental pulmonary arterial hypertension.	26463598	2015442750	x		rat	MCT60		
Borgdorff, et al.[78]	2015	Clinical symptoms of right ventricular failure in experimental chronic pressure load are associated with progressive diastolic dysfunction	25486580	2014633325	x		rat	PAB		x
Balestra, et al.[79]	2015	Increased in vivo mitochondrial oxygenation with right ventricular failure induced by pulmonary arterial hypertension: mitochondrial inhibition as driver of cardiac failure?	25645252		x		rat	MCT30 & 60		x
Bruns, et al.[80]	2015	Mitochondrial integrity in a neonatal bovine model of right ventricular dysfunction.	25416385		x		calve	hypoxia		x
Kaur, et al.[81]	2015	Poly (ADP-ribose) polymerase-1: an emerging target in right ventricle dysfunction associated with pulmonary hypertension.	25481773		x		rat	MCT60		
Aziz, et al.[82]	2015	Proteomic Profiling of Early Chronic Pulmonary Hypertension: Evidence for Both Adaptive and Maladaptive Pathology.	26246959		x		dog	DMCT		
Graham, et al.[83]	2015	Severe pulmonary hypertension is associated with altered right ventricle metabolic substrate uptake.	26115672		x		rat	SuHx		x

Khan, et al.[84]	2015	Effects of ranolazine on exercise capacity, right ventricular indices, and hemodynamic characteristics in pulmonary arterial hypertension: a pilot study.	26401256			x			PAH	
Sakao, et al.[85]	2015	Increased Right Ventricular Fatty Acid Accumulation in Chronic Thromboembolic Pulmonary Hypertension.	26356218			x			CTEPH	
Li, et al.[86]	2015	The Prognostic Value of 18F-FDG Uptake Ratio Between the Right and Left Ventricles in Idiopathic Pulmonary Arterial Hypertension.	26359560	2015437729		x			iPAH	
Drozd, et al.[87]	2016	Effects of an endothelin receptor antagonist, Macitentan, on right ventricular substrate utilization and function in a Sugen 5416/hypoxia rat model of severe pulmonary arterial hypertension.	27688036	20160703317	x		rat	SuHx		x
Brittain, et al.[88]	2016	Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension.	27006481	20160241851	x	x	mouse	BMPR2 R899X	PAH	
Talati, et al.[89]	2016	Mechanisms of Lipid Accumulation in the Bone Morphogenetic Protein Receptor Type 2 Mutant Right Ventricle.	27077479		x		mouse	BMPR2		
Joshi, et al.[90]	2016	MicroRNA-140 is elevated and mitofusin-1 is downregulated in the right ventricle of the Sugen5416/hypoxia/normoxia model of pulmonary arterial hypertension.	27422986		x		rat	SuHx		
Peters, et al.[91]	2016	Regulation of myoglobin in hypertrophied rat cardiomyocytes in experimental pulmonary hypertension.	27572699		x		rat	MCT60		
Sun, et al.[92]	2016	Reversal of right ventricular remodeling by dichloroacetate is related to inhibition of mitochondria-dependent apoptosis.	26763846	20160371500	x		rat	MCT60		x
Van der Bruggen, et al.[93]	2016	Bone Morphogenetic Protein Receptor Type 2 Mutation in Pulmonary Arterial Hypertension: A View on the Right	26984938			x			BMPR2	x

		Ventricle.								
Gupte, et al.[94]	2016	Differential Mitochondrial Function in Remodeled Right and Nonremodeled Left Ventricles in Pulmonary Hypertension.	26370778			x			PH	
Wang, et al.[95]	2016	Quantitative assessment of right ventricular glucose metabolism in idiopathic pulmonary arterial hypertension patients: a longitudinal study.	26588985	20160851284		x			iPAH	x
Sakao, et al.[96]	2016	Right ventricular sugars and fats in chronic thromboembolic pulmonary hypertension.	27323340	20160461412		x			CTEPH	
Ohira, et al.[97]	2016	Shifts in myocardial fatty acid and glucose metabolism in pulmonary arterial hypertension: a potential mechanism for a maladaptive right ventricular response.	26060207			x			PAH	
Frille, et al.[98]	2016	Thoracic [18F]fluorodeoxyglucose uptake measured by positron emission tomography/computed tomography in pulmonary hypertension.	27336898	20160485669		x			PH	
Campos, et al.[99]	2017	Effect of free and nanoencapsulated copaiba oil on monocrotaline-induced pulmonary arterial hypertension.	27798416	20160790386	x		rat	MCT60		
Liu, et al.[100]	2017	Estrogen maintains mitochondrial content and function in the right ventricle of rats with pulmonary hypertension	28320896	20170235187	x		rat	SuHx		x
He, et al.[101]	2017	Galectin-3 mediates the pulmonary arterial hypertension–induced right ventricular remodeling through interacting with NADPH oxidase 4	28431936	20170283180	x		rat	MCT60		
Cowley, et al.[102]	2017	Î±1A-Subtype Adrenergic Agonist Therapy for Failing Right Ventricle.	28822963		x		mice	bleomycin		
Tian, et al.[103]	2017	Ischemia-induced Drp1 and Fis1-mediated mitochondrial fission and right ventricular dysfunction in pulmonary hypertension	28265681	20170177715	x		rat	MCT60		
Nagy, et al.[104]	2017	Lack of ABCG2 leads to biventricular dysfunction and remodeling in response	28270772	20170166980	x		mice	PAB / hypoxia		

		to hypoxia							
Zhu, et al.[105]	2017	LOX-1 promotes right ventricular hypertrophy in hypoxia-exposed rats	28259654	20170244516	x		rat	hypoxia	
Wang, et al.[106]	2017	Oxidative profiling of the failing right heart in rats with pulmonary hypertension.	28472095	20170340497	x		rat	OVA/SuHx	
Xu, et al.[107]	2017	PPARγ Alleviates Right Ventricular Failure Secondary to Pulmonary Arterial Hypertension in Rats.	29151490		x		rat	MCT60	
Dos Santos Lacerda, et al.[108]	2017	Pterostilbene reduces oxidative stress, prevents hypertrophy and preserves systolic function of right ventricle in cor pulmonale model	28703274	20170659486	x		rat	MCT60	
Puukila, et al.[109]	2017	Secoisolariciresinol diglucoside attenuates cardiac hypertrophy and oxidative stress in monocrotaline-induced right heart dysfunction	28321539	20170209991	x		rat	MCT	
Saygin, et al.[110]	2017	Metabolic and functional evaluation of the heart and lungs in pulmonary hypertension by gated 2-[18F]-Fluoro-2-deoxy-D-glucose positron emission tomography	28597761	20170459867		x			PH
Siqueira, et al.[111]	2018	Effects of ovariectomy in antioxidant defence systems in right ventricle of female rats with pulmonary arterial hypertension induced by monocrotaline.	28854338		x		rat	MCT	

Table S2. Meta-regression analyses: variables versus duration of RV pressure load.

	coefficient	constant	std. error	t	P > |t|	[95% conf. interval]	
FDG-uptake	-0.006	1.831118	0.028237	-0.21	0.851	-0.12751	0.115473
GLUT1 mRNA	0.007318	1.338181	0.017441	0.42	0.681	-0.03009	0.044725
GLUT1 protein	-0.06177	5.544784	0.193256	-0.32	0.780	-0.89329	0.769742
GLUT4 mRNA	-0.08868	-0.1779	0.094733	-0.94	0.385	-0.32048	0.143124
GLUT4 protein	0.062796	-1.92728	0.044244	1.42	0.251	-0.07801	0.2036
HK1 mRNA	-0.41346	20.52151	0.203145	-2.04	0.081	-0.89382	0.066904
HK2 mRNA	0.013838	-0.26506	0.035005	0.4	0.703	-0.06688	0.09456
CTP1B mRNA	-0.26705	9.571756	0.071064	-3.76	**0.033**	-0.49321	-0.0409
mitochondrial content	-0.0066	-0.41463	0.009553	-0.69	0.507	-0.02821	0.015005
mitochondrial content (first six weeks only)	*-0.12221*	*2.461455*	*0.025414*	*-4.81*	***0.002***	*-0.1823*	*-0.06211*
PDH mRNA	-0.0066	-0.26024	0.071658	-0.09	0.935	-0.31492	0.301721
PDK4 mRNA	-0.20665	0.005799	0.178042	-1.16	0.310	-0.70097	0.287676
PGC1a mRNA	-0.06271	0.634076	0.021666	-2.89	**0.044**	-0.12287	-0.00256
PGC1a protein	-0.04477	0.977281	0.03338	-1.34	0.272	-0.151	0.061461
PPAR mRNA	-0.03096	0.785598	0.023265	-1.33	0.232	-.0878866	0.025968
MCAD mRNA	-0.10478	-3.09365	0.096481	-1.09	0.313	-0.33292	0.123366
MCAD protein	0.120205	-5.58791	0.080062	1.5	0.272	-0.22427	0.464684
resp. cap. Glucose - ADP driven	-0.00781	-0.53042	0.009609	-0.81	0.566	-0.1299	0.114282
resp. cap. Glucose - whole cells	-0.11876	3.300385	0.114537	-1.04	0.409	-0.61157	0.374057
resp. cap. FA - ADP driven	-0.00753	-0.49098	0.010332	-0.73	0.519	-0.04041	0.025351

Significant p-values shown in **bold**.

Table S3. Meta-regression analyses: variables versus degree of RV pressure load.

	coefficient	constant	std. error	t	P > |t|	[95% conf. interval]	
FDG-uptake	-0.605857	3.8261	1.127987	-0.54	0.628	-4.19562	2.983902
GLUT1 mRNA	-0.097231	1.875722	0.258773	-0.38	0.771	-3.38525	3.19079
GLUT4 protein	0.6982679	-0.7738904	0.884316	0.79	0.460	-1.46558	2.86211
HK1 mRNA	2.672385	-14.20094	1.530079	1.75	0.223	-3.91101	9.255784
HK2 mRNA	0.2727004	-2.639479	0.392468	0.69	0.518	-0.73617	1.281572
mitochondrial content	-0.490853	0.6067835	0.163592	-3	**0.040**	-0.94506	-0.03665
PDH mRNA	-0.19941	1.375868	0.195707	-1.02	0.415	-1.04147	0.642648
PDK4 protein	-5.779816	6.268431	8.17396	-0.71	0.608	-109.64	98.0802
PDK1 mRNA	0.2356872	-2.020017	0.125199	1.88	0.311	-1.35512	1.826494
PDK1 protein	1.077672	-0.6647883	2.190228	0.49	0.709	-26.7518	28.90716
MCAD mRNA	1.856523	-19.68273	5.871176	0.32	0.782	-23.4051	27.11816
MCAD protein	-0.287837	0.7897496	0.113183	-2.54	0.239	-1.72596	1.150285
resp. cap. Glucose - ADP driven	0.2589947	-1.225371	0.286097	0.91	0.432	-0.65149	1.169482
resp. cap. FA - ADP driven	-0.257863	0.0167995	0.519064	-0.5	0.669	-2.49122	1.975488

Significant p-values shown in **bold**.

Table S4. Level of significance of meta-analysis and meta-regression.

	mRNA expression level				*protein expression level*			
parameter	**meta-analysis**	**model effect** *(increased compared)*	**duration effect**	**effect of degree of pressure load**	**meta-analysis**	**model effect** *(increased compared)*	**duration effect**	**effect of degree of pressure load**
GLUT1	↑ (0.000)	~	~	~	↑ (0.009)	MCT vs. hypoxia, PAB and FHR	~	~
GLUT4	~	~	~	~	~	~	~	~
CTP1B	~	~	↓ (0.033)	N/A	N/A	N/A	N/A	N/A
HK1	↑ (0.000)	~	↘ (0.081)	~	N/A	N/A	N/A	N/A
HK2	~	~	~	~	N/A	N/A	N/A	N/A
PDH	~	~	~	~	↘ (0.123)	~	~	N/A
PDK4	↘ (0.110)	~	~	~	~	~	N/A	-
PDK1	N/A	N/A	N/A	~	~	~	N/A	~
PDK2	N/A	N/A	N/A	N/A	~	~	N/A	N/A
MCAD	↓ (0.000)	~	~	~	↘ (0.141)	~	~	~
PGC1α	↓ (0.008)	~	↓ (0.044)	~	~	MCT vs. SuHx	~	N/A
PPARα	~	~	~	N/A	N/A	N/A	N/A	N/A

in vivo measurements				
parameter	**meta-analysis**	**model effect** *(increased compared)*	**duration effect**	**effect of degree of pressure load**
FDG-uptake	↑ (0.000)	~	~	~
Glycolysis – whole cells (i.e. Langendorf, Seahorse)	↑ (0.000)	~	N/A	N/A
Respiratory capacity, carbohydrates – isolated mitochondria (i.e. Oroboros, Clark-type)	↘ (0.085)	~	~	~
Respiratory capacity, carbohydrates – whole cells (i.e. Langendorf, Seahorse)	↘ (0.082)	MCT vs. PAB and FHR	~	N/A
Respiratory capacity, fatty acids – isolated mitochondria (i.e. Oroboros, Clark-type)	↓ (0.001)	~	↘ (0.130)	~
Respiratory capacity, fatty acids – whole cells (i.e. Langendorf, Seahorse)	~	PAB vs. SuHx.	N/A	N/A

combined measurements				
parameter	**meta-analysis**	**model effect**	**duration effect**	**effect of degree of pressure load**
Mitochondrial content	~	~	~ (*≤6 days* (0.002))	~

↑significant increase or positive relation; ↓ significant decrease or negative relation; ↗positive trend (p<0.15); ↘ negative trend (p<0.15); ~ unchanged.

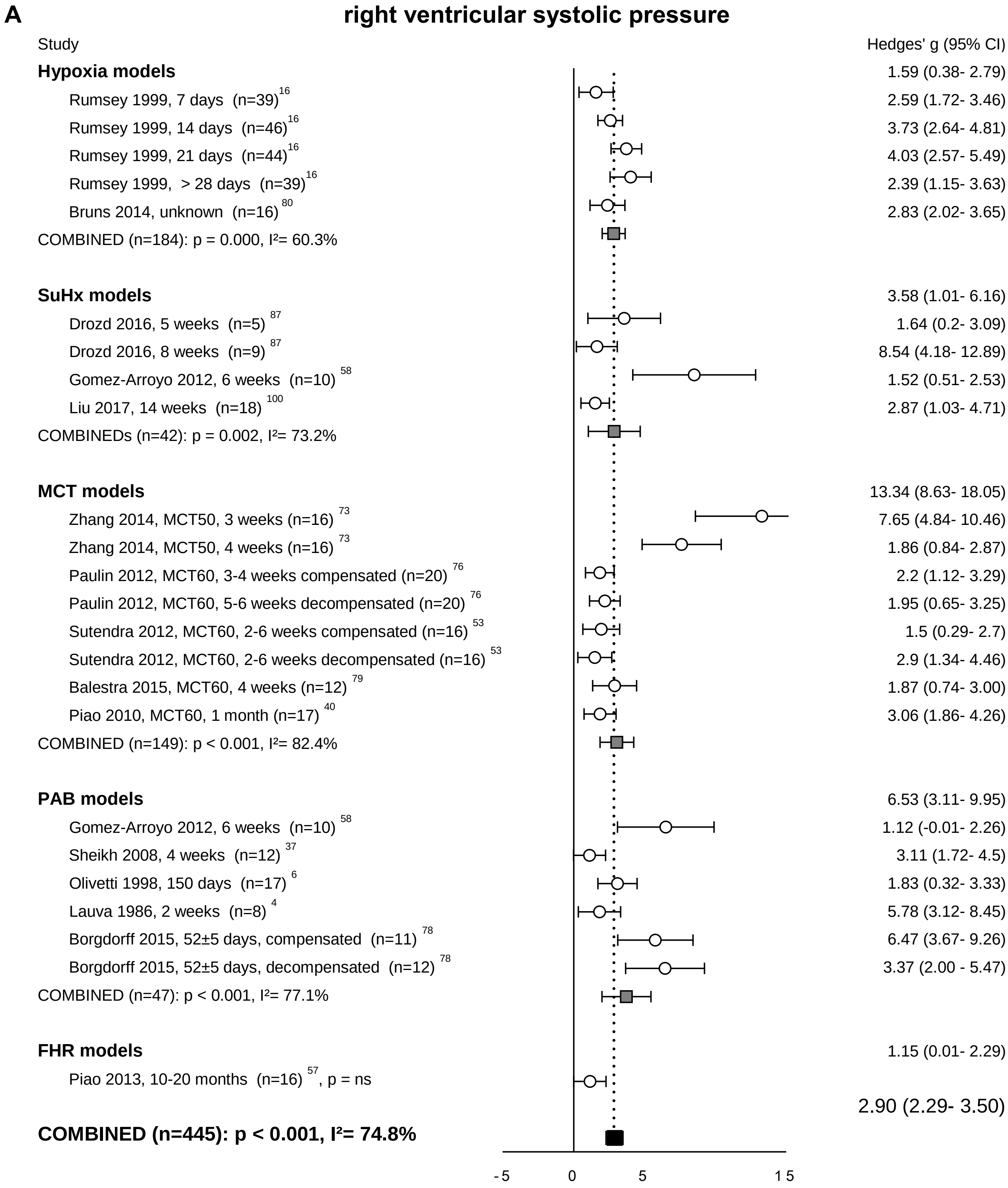
Table S5. Overview of Hedges' g for metabolic parameters in models of RV pressure load subjected to therapeutic interventions.

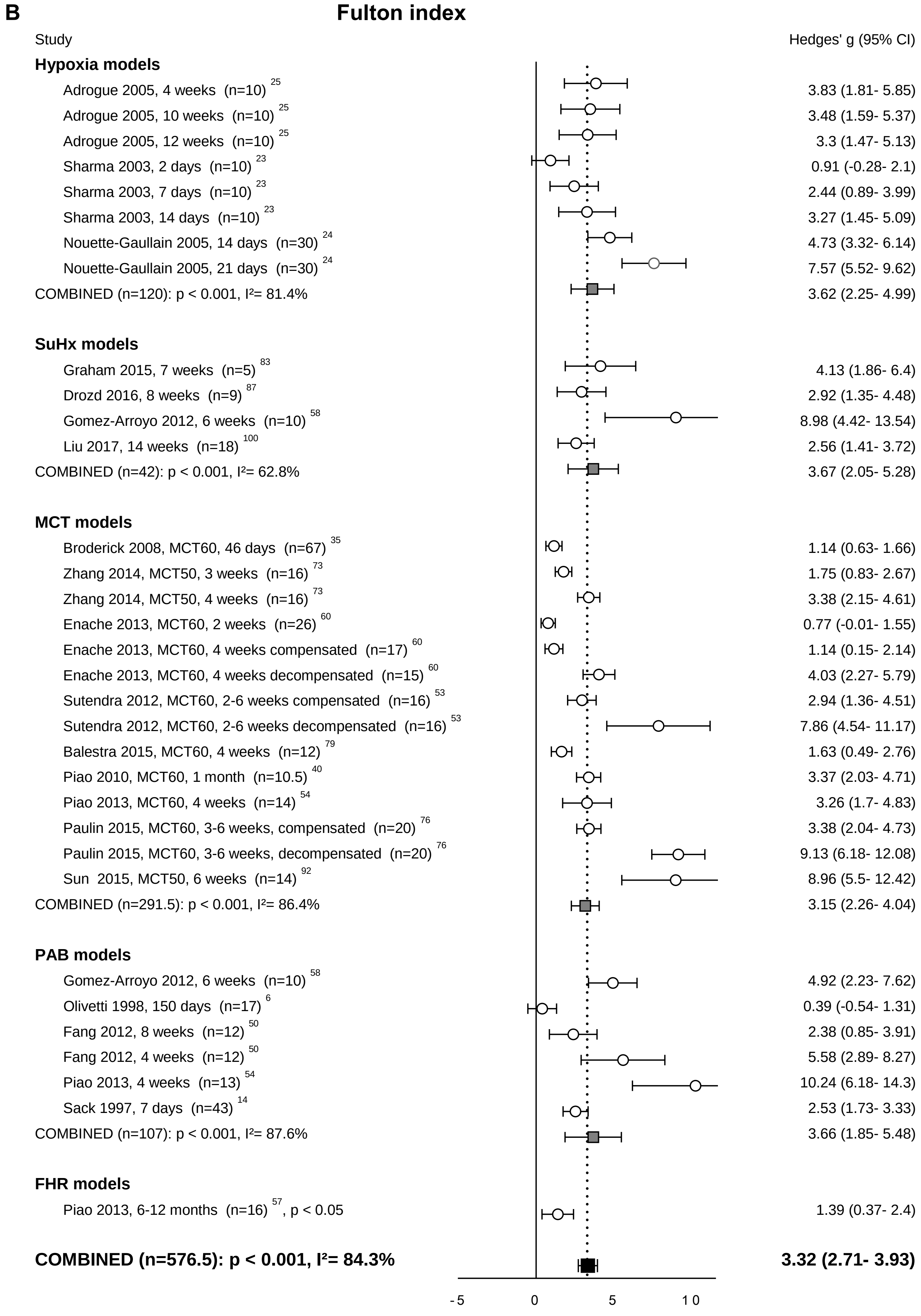
							Hedges' g																	
animal	#	Year	Author	Hit duration	Model	Therapie	GLUT1 - mRNA	GLUT1 - protein	GLUT4 - protein	FDG-uptake	CPT1B - mRNA	CPT1A - protein	HK1 - mRNA	HK1 - protein	HK2 - mRNA	PDH - activity	PDHa1 - protein	PDK4 - mRNA	PDK4 - protein	PDK1 - mRNA	PDK1 - protein	PDK2 - mRNA	PDK2 - protein	PGC1alpha - protein
Rat	19949938	2010	Piao[40]	1 month	MCT60	DCA	-1.68	-2.58		-0.41						-0.99								
Rat	23247844	2012	Piao[57]	10-20 months	FHR	DCA, acute treatment																		
Rat	23247844	2012	Piao[57]	10-20 months	FHR	DCA, chronic treatment (6 months)	-1.44				0.01				-2.74*	4.13*		-1.51*	0.58	0.36	0.48	0.60	-0.95	
Rat	26763846	2016	Sun[92]	6 weeks	MCT	DCA 50mg/kg											1.62*		-6.14*		0.47		-1.78*	
Rat	26763846	2016	Sun[92]	6 weeks	MCT	DCA 150mg/kg											3.27*		-0.86*		0.40		-2.6*	
Rat	26763846	2016	Sun[92]	6 weeks	MCT	DCA 200 mg/kg											3.38*		-6.89*		0.33		-3.20*	
Rat	23794090	2013	Piao[54]	4 weeks	MCT	DON	-2.19						-1.10			1.14*								
Rat	27688036	2016	Drozd[87]	9 weeks	SuHx	ERA			-2.67*	-1.20														
Rat	28320896	2017	Liu[100]	14 weeks	SuHx	oestrogen																		3.36*
Rat	21874543	2012	Fang[50]	4 weeks	PAB	RAN	-1.46*	-0.45604				-1.83*	-2.55*	-0.46	-0.08	2.01*								
Rat	21874543	2012	Fang[50]	4 weeks	PAB	RAN, in vitro																		
Rat	21874543	2012	Fang[50]	8 weeks	PAB	TMZ	-1.30*	-1.33*				-1.41*	-1.18*	-0.18	-0.18	1.36*								
Rat	21874543	2012	Fang[50]	8 weeks	PAB	TMZ, in vitro																		

animal	#	Year	Author	Hit duration	Model	Therapie	Hedges'g Glycolysis	Mitochondrial resp. capacity Glucose, isolated mitochondria	Mitochondrial resp. capacity Glucose, Langendorf	Mitochondrial resp. capacity Glucose, Seahorse	Mitochondrial resp. capacity fatty acids, isolated mitochondria	Mitochondrial resp. capacity FA, Langendorf	Mitochondrial resp. capacity FA, Seahorse	Mitochondrial content	Fulton
Rat	19949938	2010	Piao[40]	1 month	MCT60	DCA	0.65		3.20*						-1.59*
Rat	23247844	2012	Piao[57]	10-20 months	FHR	DCA, acute treatment	-0.79		3.51*			-1.22*			
Rat	23247844	2012	Piao[57]	10-20 months	FHR	DCA, chronic treatment (6 months)	-0.71			0.35			0.40		
Rat	26763846	2016	Sun[92]	6 weeks	MCT	DCA 50mg/kg									-2.72*
Rat	26763846	2016	Sun[92]	6 weeks	MCT	DCA 150mg/kg									-5.83*
Rat	26763846	2016	Sun[92]	6 weeks	MCT	DCA 200 mg/kg									-5.97*
Rat	23794090	2013	Piao[54]	4 weeks	MCT	DON									-0.92
Rat	27688036	2016	Drozd[87]	9 weeks	SuHx	ERA									
Rat	28320896	2017	Liu[100]	14 weeks	SuHx	oestrogen		0.38			0.36			-0.01	-1.01*
Rat	21874543	2012	Fang[50]	4 weeks	PAB	RAN	-0.99			2.98*		-1.34*			-2.16*
Rat	21874543	2012	Fang[50]	4 weeks	PAB	RAN, in vitro						-14.63*			
Rat	21874543	2012	Fang[50]	8 weeks	PAB	TMZ	-1.47*			2.43 * (10 mM gluc), 1.99* (5mM gluc).		-1.28*	-7.29*		-1.79*
Rat	21874543	2012	Fang[50]	8 weeks	PAB	TMZ, in vitro						-4.18*			

** p mentioned in study < 0.05*

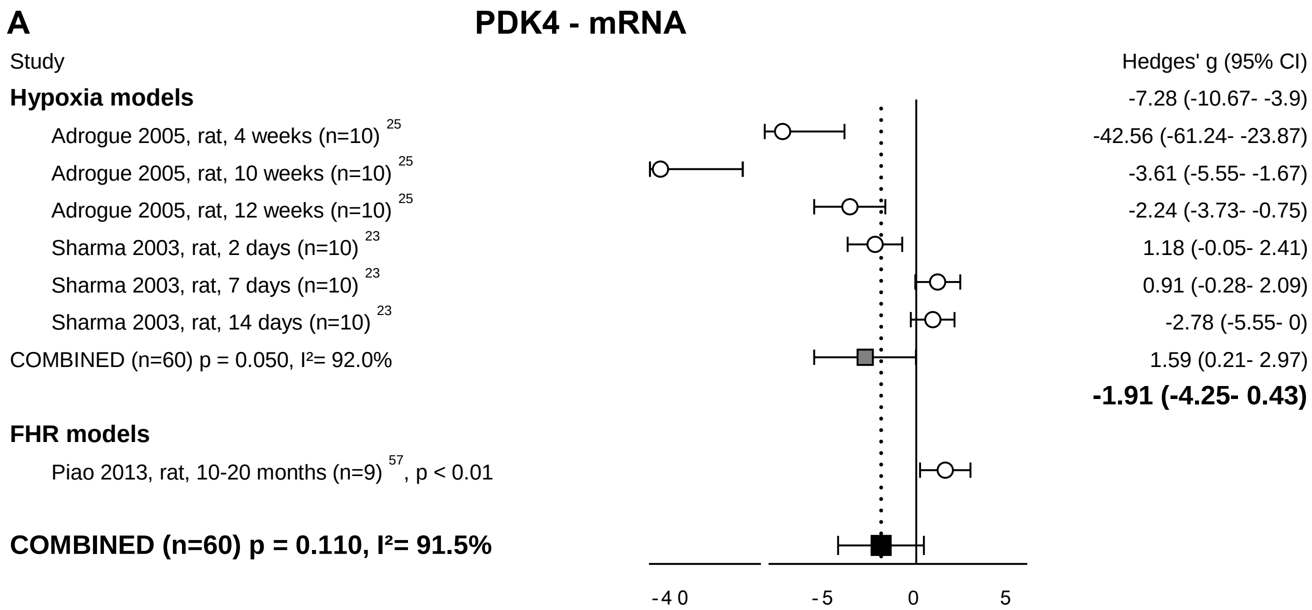
Figure S1. Models of increased pressure load.

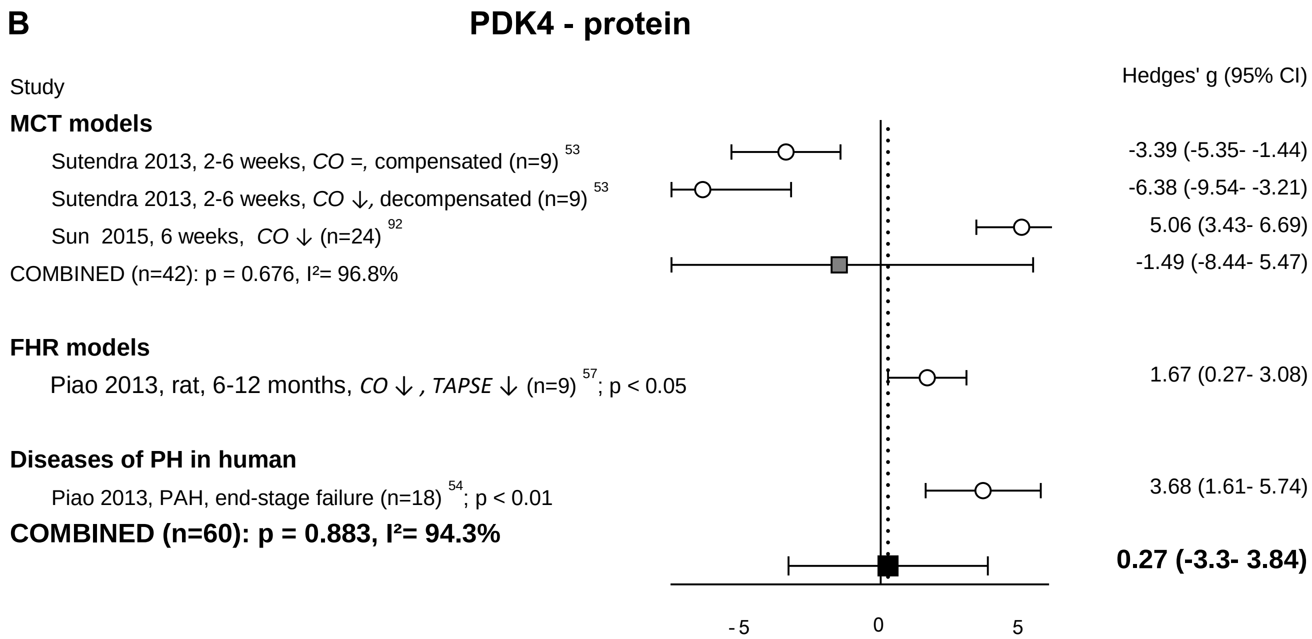


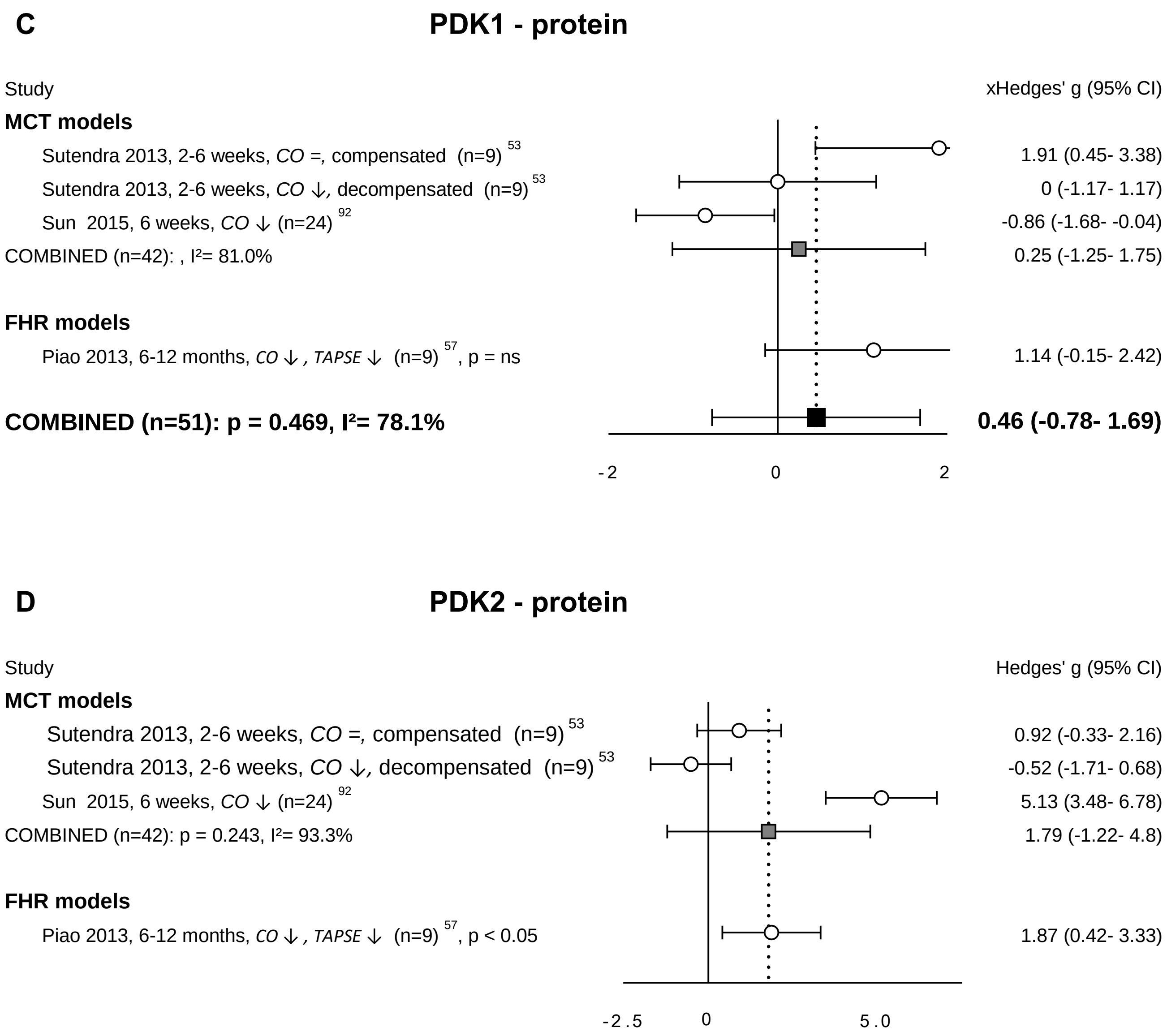

B
Fulton index
Study
Hedges' g (95% CI)
Hypoxia models
Adrogue 2005, 4 weeks (n=10) [25]
3.83 (1.81- 5.85)
Adrogue 2005, 10 weeks (n=10) [25]
3.48 (1.59- 5.37)
Adrogue 2005, 12 weeks (n=10) [25]
3.3 (1.47- 5.13)
Sharma 2003, 2 days (n=10) [23]
0.91 (-0.28- 2.1)
Sharma 2003, 7 days (n=10) [23]
2.44 (0.89- 3.99)
Sharma 2003, 14 days (n=10) [23]
3.27 (1.45- 5.09)
Nouette-Gaullain 2005, 14 days (n=30) [24]
4.73 (3.32- 6.14)
Nouette-Gaullain 2005, 21 days (n=30) [24]
7.57 (5.52- 9.62)
COMBINED (n=120): p < 0.001, I²= 81.4%
3.62 (2.25- 4.99)
SuHx models
Graham 2015, 7 weeks (n=5) [83]
4.13 (1.86- 6.4)
Drozd 2016, 8 weeks (n=9) [87]
2.92 (1.35- 4.48)
Gomez-Arroyo 2012, 6 weeks (n=10) [58]
8.98 (4.42- 13.54)
Liu 2017, 14 weeks (n=18) [100]
2.56 (1.41- 3.72)
COMBINED (n=42): p < 0.001, I²= 62.8%
3.67 (2.05- 5.28)
MCT models
Broderick 2008, MCT60, 46 days (n=67) [35]
1.14 (0.63- 1.66)
Zhang 2014, MCT50, 3 weeks (n=16) [73]
1.75 (0.83- 2.67)
Zhang 2014, MCT50, 4 weeks (n=16) [73]
3.38 (2.15- 4.61)
Enache 2013, MCT60, 2 weeks (n=26) [60]
0.77 (-0.01- 1.55)
Enache 2013, MCT60, 4 weeks compensated (n=17) [60]
1.14 (0.15- 2.14)
Enache 2013, MCT60, 4 weeks decompensated (n=15) [60]
4.03 (2.27- 5.79)
Sutendra 2012, MCT60, 2-6 weeks compensated (n=16) [53]
2.94 (1.36- 4.51)
Sutendra 2012, MCT60, 2-6 weeks decompensated (n=16) [53]
7.86 (4.54- 11.17)
Balestra 2015, MCT60, 4 weeks (n=12) [79]
1.63 (0.49- 2.76)
Piao 2010, MCT60, 1 month (n=10.5) [40]
3.37 (2.03- 4.71)
Piao 2013, MCT60, 4 weeks (n=14) [54]
3.26 (1.7- 4.83)
Paulin 2015, MCT60, 3-6 weeks, compensated (n=20) [76]
3.38 (2.04- 4.73)
Paulin 2015, MCT60, 3-6 weeks, decompensated (n=20) [76]
9.13 (6.18- 12.08)
Sun 2015, MCT50, 6 weeks (n=14) [92]
8.96 (5.5- 12.42)
COMBINED (n=291.5): p < 0.001, I²= 86.4%
3.15 (2.26- 4.04)
PAB models
Gomez-Arroyo 2012, 6 weeks (n=10) [58]
4.92 (2.23- 7.62)
Olivetti 1998, 150 days (n=17) [6]
0.39 (-0.54- 1.31)
Fang 2012, 8 weeks (n=12) [50]
2.38 (0.85- 3.91)
Fang 2012, 4 weeks (n=12) [50]
5.58 (2.89- 8.27)
Piao 2013, 4 weeks (n=13) [54]
10.24 (6.18- 14.3)
Sack 1997, 7 days (n=43) [14]
2.53 (1.73- 3.33)
COMBINED (n=107): p < 0.001, I²= 87.6%
3.66 (1.85- 5.48)
FHR models
Piao 2013, 6-12 months (n=16) [57], p < 0.05
1.39 (0.37- 2.4)
COMBINED (n=576.5): p < 0.001, I²= 84.3%
3.32 (2.71- 3.93)
-5
0
5
10

Forest plots of right ventricular systolic pressure (A) and Fulton index (B). Data are presented as Hedges' g (95% confidence interval). Combined Hedges' g are presented as squares: grey representing Hedges' g of a specific model, black representing Hedges' g of all included studies. Bars represent 95% confidence interval. *CI = confidence interval. n = number of included animals.* i^2 = *level of heterogeneity.*

Figure S2. Forest plots of expression of PDK isoenzymes.

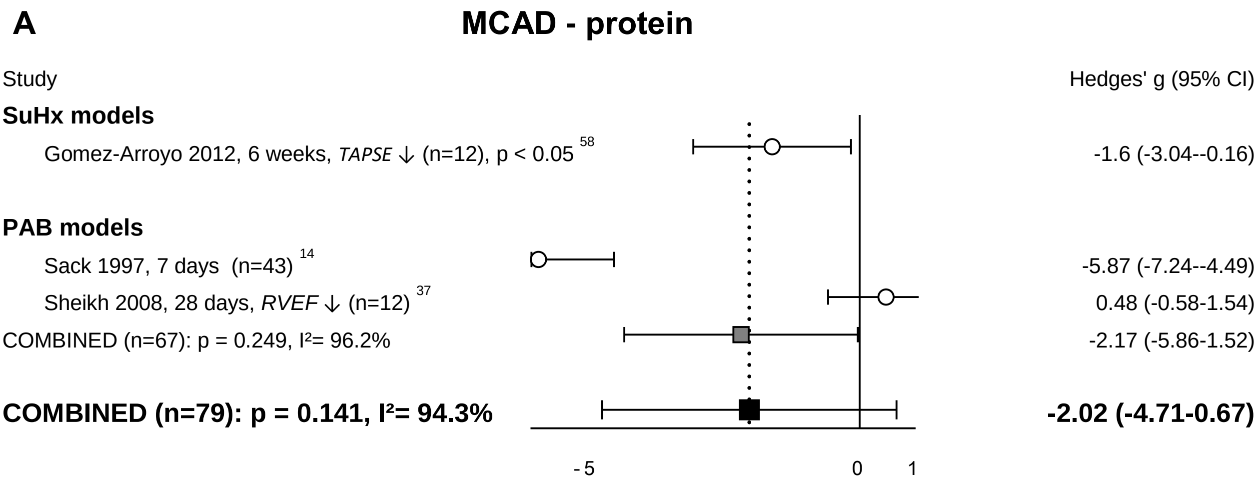






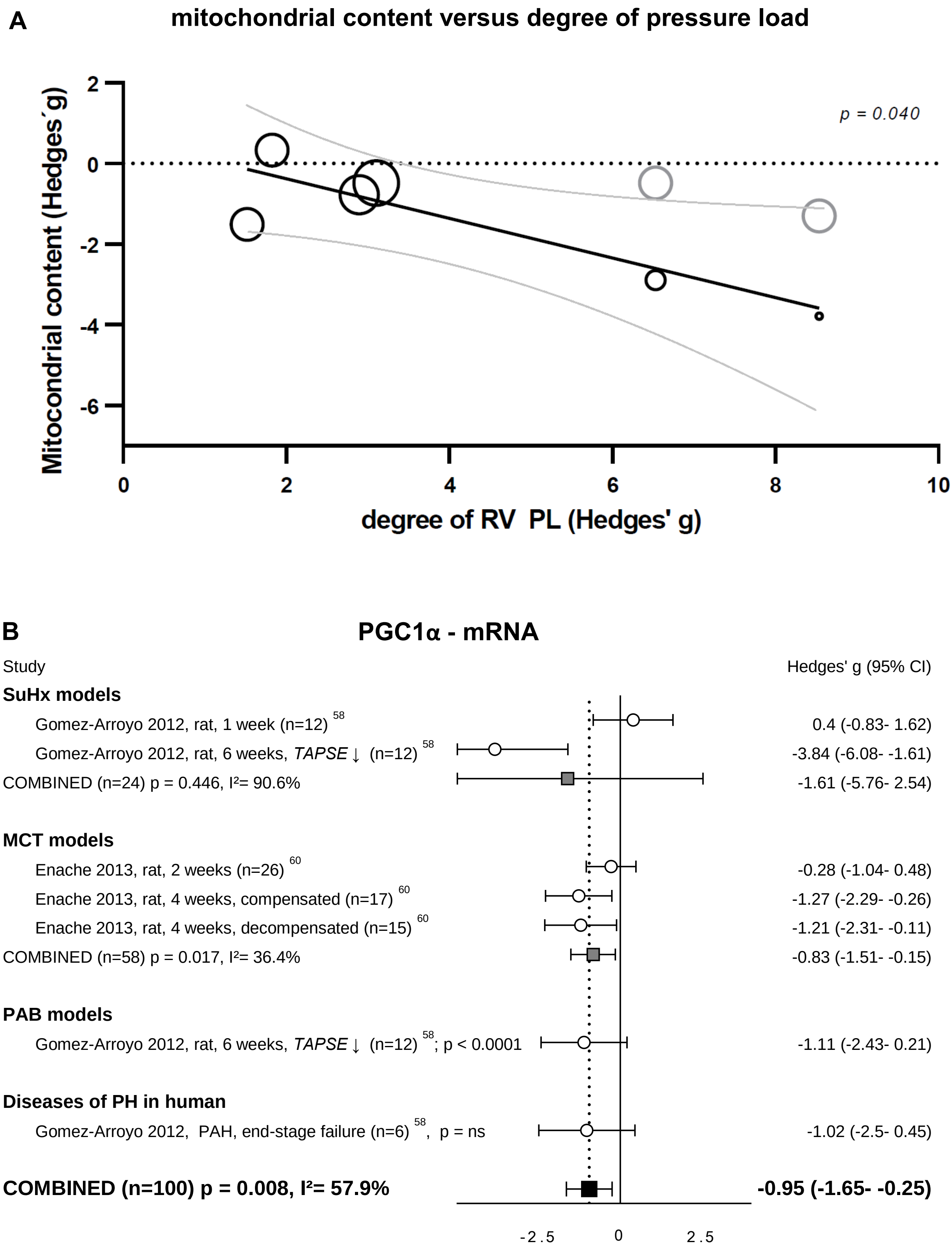
PDK4 at both mRNA (A) and protein level (B), and PDK1 (C) and PDK2 (D) at protein level. Bars represent 95% confidence interval. PDK = pyruvate dehydrogenase kinase. *CO* = cardiac output, *CI* = cardiac index, *TAPSE* = tricuspid annular plane systolic movement, *RVEF* = RV ejection fraction, ↓ = decreased, "=" = not statistically significant affected. 95% CI = 95% confidence interval, n = number of included animals, i^2 = level of heterogeneity, x = not included in meta-analysis.

Figure S3. Forest plot MCAD at protein level.

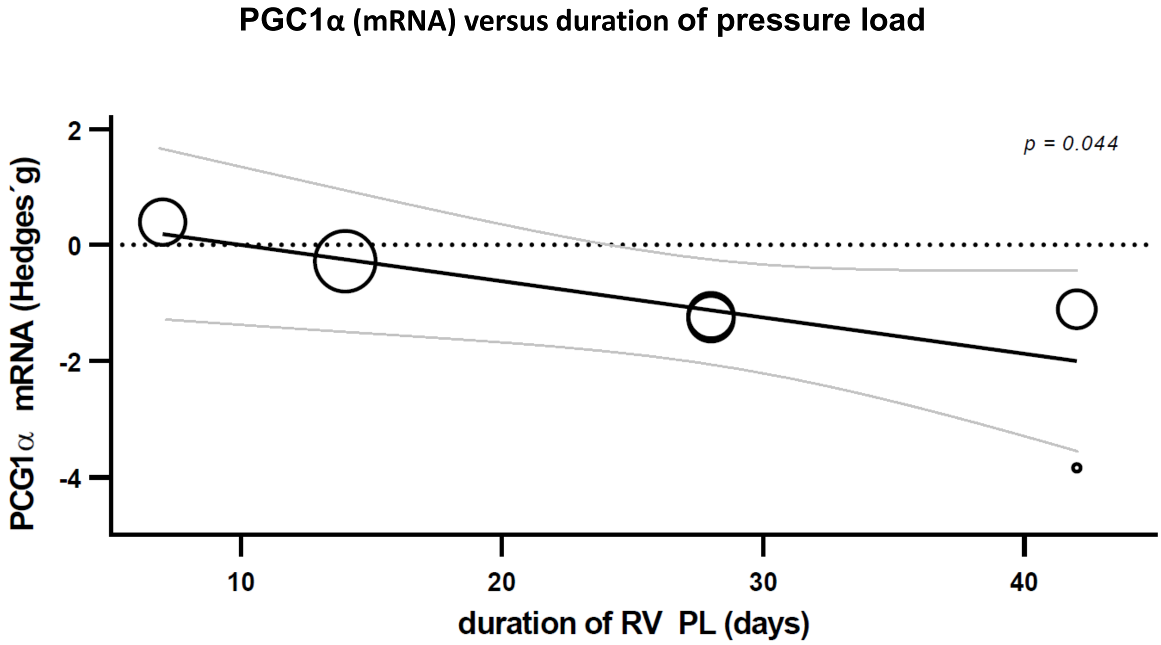


Bars represent 95% confidence interval. MCAD = medium chain acyl CoA dehydrogenase. *CO* = cardiac output, *CI* = cardiac index, *TAPSE* = tricuspid annular plane systolic movement, *RVEF* = RV ejection fraction, ↓ = decreased, "=" = not statistically significant affected. 95% CI = 95% confidence interval, n = number of included animals, i^2 = level of heterogeneity, x = not included in meta-analysis.

Figure S4. Regulators of metabolism.

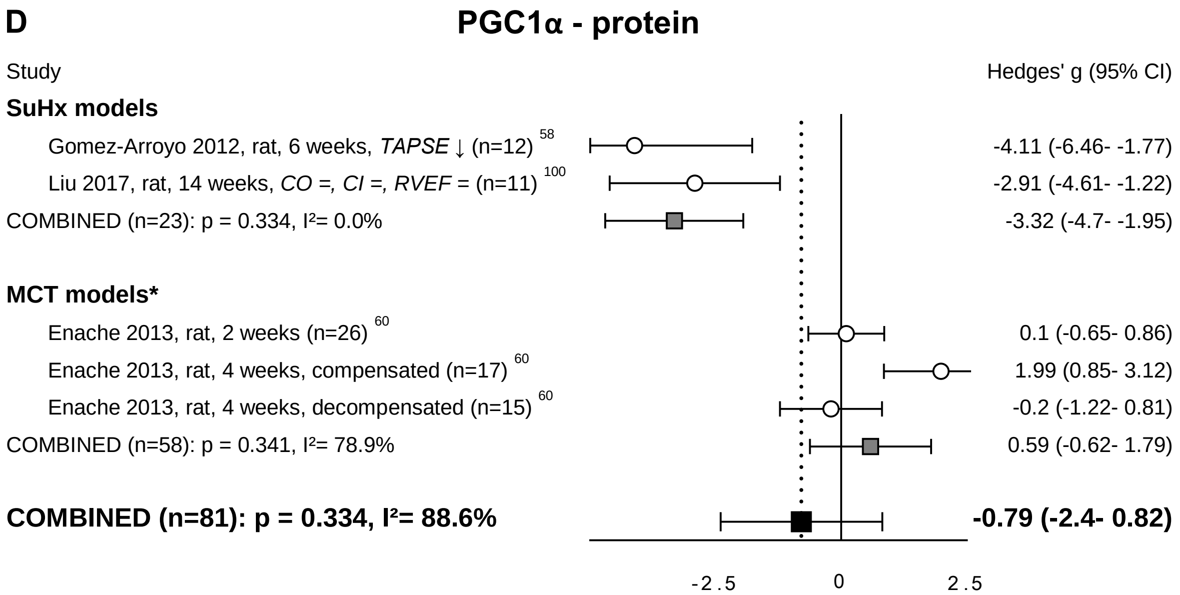


C

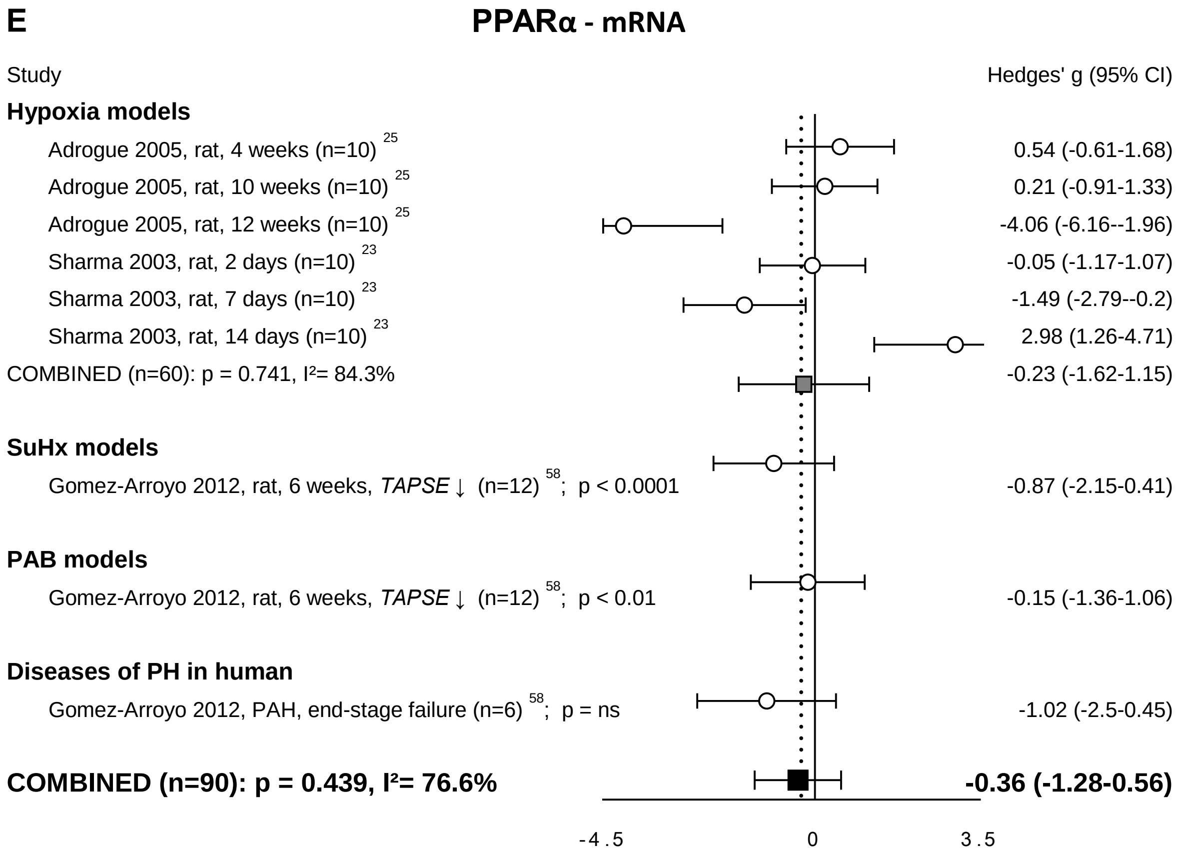


PGC1α (mRNA) versus duration of pressure load
p = 0.044
2
0
-2
-4
PCG1α mRNA (Hedges´g)
10
20
30
40
duration of RV PL (days)

D



PGC1α - protein
Study
Hedges' g (95% CI)
SuHx models
Gomez-Arroyo 2012, rat, 6 weeks, TAPSE ↓ (n=12) 58
-4.11 (-6.46- -1.77)
Liu 2017, rat, 14 weeks, CO =, CI =, RVEF = (n=11) 100
-2.91 (-4.61- -1.22)
COMBINED (n=23): p = 0.334, I²= 0.0%
-3.32 (-4.7- -1.95)
MCT models*
Enache 2013, rat, 2 weeks (n=26) 60
0.1 (-0.65- 0.86)
Enache 2013, rat, 4 weeks, compensated (n=17) 60
1.99 (0.85- 3.12)
Enache 2013, rat, 4 weeks, decompensated (n=15) 60
-0.2 (-1.22- 0.81)
COMBINED (n=58): p = 0.341, I²= 78.9%
0.59 (-0.62- 1.79)
COMBINED (n=81): p = 0.334, I²= 88.6%
-0.79 (-2.4- 0.82)
-2.5
0
2.5



Meta-regression of mitochondrial content with degree of RV pressure load (A). PGC1α gene expression(B) and its relation with duration of pressure load shown by meta-regression in a bubble plot (C). Forrest plot of PGC1α protein expression (D). Forrest plot of PPARα gene expression (E). Data are presented as Hedges' g. Combined Hedges' g are presented as squares: grey representing Hedges' g of a specific model, black representing Hedges' g of all included studies. Bars represent 95% confidence interval. Bubble size represents relative study precision, calculation based on standard deviation. Black line represents regression line, grey lines represents 95% confidence interval. CO = cardiac output, CI = cardiac index, TAPSE = tricuspid annular plane systolic movement, RVEF = RV ejection fraction, ↓ = decreased, "=" = not statistically significant affected. 95% CI = 95% confidence interval, n = number of included animals, i^2 = level of heterogeneity. * = significantly ($p < 0.05$) increased compared to SuHx-model.

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