

# VU Research Portal

## Striated muscle dysfunction in Pulmonary Arterial Hypertension

Manders, E.

2015

### **document version**

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

### **citation for published version (APA)**

Manders, E. (2015). *Striated muscle dysfunction in Pulmonary Arterial Hypertension*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

### **General rights**

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

### **E-mail address:**

[vuresearchportal.ub@vu.nl](mailto:vuresearchportal.ub@vu.nl)

# Bibliography

- [1] Agten, A., Maes, K., Thomas, D., Cielen, N., Van Hees, H. W. H., Dekhuijzen, R. P. N., Decramer, M., and Gayan-Ramirez, G. (2012). Bortezomib partially protects the rat diaphragm from ventilator-induced diaphragm dysfunction. *Crit Care Med*, 40(8):2449–55.
- [2] Ahn, B., Empinado, H. M., Al-Rajhi, M., Judge, A. R., and Ferreira, L. F. (2013). Diaphragm atrophy and contractile dysfunction in a murine model of pulmonary hypertension. *PLoS one*, 8(4):1–7.
- [3] Baldwin, K. M. and Haddad, F. (2001). Invited Review: Effects of different activity and inactivity paradigms on myosin heavy chain gene expression in striated muscle. *J Appl Physiol*, 90:345–357.
- [4] Bando, K., Keenan, R. J., Paradis, I. L., Konishi, H., Komatsu, K., Hardesty, R. L., and Griffith, B. P. (1994). Impact of pulmonary hypertension on outcome after single-lung transplantation. *Ann Thorac Surg*, 58(5):1336–42.
- [5] Batt, J., Ahmed, S. S., Correa, J., Bain, A., Granton, J., and Shadly Ahmed, S. (2014). Skeletal muscle dysfunction in idiopathic pulmonary arterial hypertension. *Am J Respir Cell Mol Biol*, 50(1):74–86.
- [6] Bauer, R., Dehnert, C., Schoene, P., Filusch, A., Bartsch, P., Borst, M. M., Katus, H. A., and Meyer, F. J. (2007). Skeletal muscle dysfunction in patients with idiopathic pulmonary arterial hypertension. *Respir Med*, 101:2366–2369.
- [7] Beckman, J. S. and Koppenol, W. H. (1996). Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. *Am J Physiol*, 271:C1424—C1437.
- [8] Benza, R. L., Miller, D. P., Gomberg-Maitland, M., Frantz, R. P., Foreman, A. J., Coffey, C. S., Frost, A., Barst, R. J., Badesch, D. B., Elliott, C. G., Liou, T. G., and McGoon, M. D. (2010). Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation*, 122(2):164–72.
- [9] Birsan, T., Kranz, A., Mares, P., Artemiou, O., Taghavi, S., Zuckermann, A., and Klepetko, W. (1999). Transient Left Ventricular Failure Following Bilateral Lung Transplantation for Pulmonary Hypertension. *J Heart Lung Transplant*, 2498(98):304–309.
- [10] Bottinelli, R., Canepari, M., Reggiani, C., and Stienen, G. J. (1994). Myofibrillar ATPase activity during isometric contraction and isomyosin composition in rat single skinned muscle fibres. *J Physiol*, 481 ( Pt 3:663–675.
- [11] Brenner, B. (1988). Effect of Ca<sup>2+</sup> on cross-bridge turnover kinetics in skinned single rabbit psoas fibers: implications for regulation of muscle contraction. *Proc Natl Acad Sci*, 85(9):3265–3269.
- [12] Brenner, B. and Eisenberg, E. (1986). Rate of force generation in muscle: Correlation with actomyosin ATPase activity in solution. *Proc Natl Acad Sci*, 83:3542–3546.
- [13] Bristow, M. R., Minobe, W., Rasmussen, R., Larrabee, P., Skerl, L., Klein, J. W., Anderson, F. L., Murray, J., Mestroni, L., and Karwande, S. V. (1992). Beta-adrenergic neuroeffector abnormalities in the failing human heart are produced by local rather than systemic mechanisms. *J Clin Invest*, 89(3):803–15.
- [14] Canton, M., Neverova, I., Menabo, R., Eyk, J. V., and Lisa, F. D. (2004). Evidence of myofibrillar protein oxidation induced by postischemic reperfusion in isolated rat hearts. *Am J Physiol Heart Circ Physiol*, 286(3):H870—H877.
- [15] Chandra, M., Mamidi, R., Ford, S., Hidalgo, C., Witt, C., Ottenheijm, C., Labeit, S., and Granzier, H. (2009). Nebulin alters cross-bridge cycling kinetics and increases thin filament activation: a novel mechanism for increasing tension and reducing tension cost. *J Biol Chem*, 284(45):30889–96.
- [16] Dall'Ago, P., Chiappa, G. R. S., Guths, H., Stein, R., and Ribeiro, J. P. (2006). Inspiratory muscle

- 
- training in patients with heart failure and inspiratory muscle weakness: a randomized trial. *J Am Coll Cardiol*, 47(4):757–63.
- [17] D'Antona, G., Pellegrino, M. A., Adami, R., Rossi, R., Carlizzi, C. N., Canepari, M., Saltin, B., and Bottinelli, R. (2003). The effect of ageing and immobilization on structure and function of human skeletal muscle fibres. *J Physiol*, 552:499–511.
- [18] de Man, F. S., Handoko, M. L., Groepenhoff, H., van 't Hul, A. J., Abbink, J., Koppers, R. J., Grotjohan, H. P., Twisk, J. W., Bogaard, H. J., Boonstra, A., Postmus, P. E., Westerhof, N., van der Laarse, W. J., and Vonk-Noordegraaf, A. (2009). Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. *Eur Resp J*, 34:669–675.
- [19] de Man, F. S., Handoko, M. L., Guignabert, C., Bogaard, H. J., and Vonk-Noordegraaf, A. (2013). Neurohormonal axis in patients with pulmonary arterial hypertension: friend or foe? *Am J Respir Crit Care Med*, 187(1):14–9.
- [20] de Man, F. S., Handoko, M. L., van Ballegoij, J. J. M., Schaliij, I., Bogaards, S. J. P., Postmus, P. E., van der Velden, J., Westerhof, N., Paulus, W. J., and Vonk-Noordegraaf, A. (2012a). Bisoprolol delays progression towards right heart failure in experimental pulmonary hypertension. *Circ Heart Fail*, 5(1):97–105.
- [21] de Man, F. S., Tu, L., Handoko, M. L., Rain, S., Ruiter, G., François, C., Schaliij, I., Dorfmueller, P., Simonneau, G., Fadel, E., Perros, F., Boonstra, A., Postmus, P. E., van der Velden, J., Vonk-Noordegraaf, A., Humbert, M., Eddahibi, S., and Guignabert, C. (2012b). Dysregulated renin-angiotensin-aldosterone system contributes to pulmonary arterial hypertension. *Am J Respir Crit Care Med*, 186(8):780–9.
- [22] de Man, F. S., van Hees, H. W. H., Handoko, M. L., Niessen, H. W., Schaliij, I., Humbert, M., Dorfmueller, P., Mercier, O., Bogaard, H.-J., Postmus, P. E., Westerhof, N., Stienen, G. J. M., van der Laarse, W. J., Vonk-Noordegraaf, A., and Ottenheijm, C. A. C. (2011). Diaphragm muscle fiber weakness in pulmonary hypertension. *Am J Respir Crit Care Med*, 183(10):1411–1418.
- [23] Deboeck, G., Niset, G., Lamotte, M., Vachiéry, J. L., and Naeije, R. (2004). Exercise testing in pulmonary arterial hypertension and in chronic heart failure. *Eur Respir J*, 23(5):747–751.
- [24] Doorduyn, J., Sinderby, C. A., Beck, J., Stegeman, D. F., van Hees, H. W. H., van der Hoeven, J. G., and Heunks, L. M. A. (2012). The calcium sensitizer levosimendan improves human diaphragm function. *Am J Respir Crit Care Med*, 185(1):90–5.
- [25] Dorfman, T. A., Levine, B. D., Tillery, T., Peshock, R. M., Hastings, J. L., Schneider, S. M., Macias, B. R., Biolo, G., and Hargens, A. R. (2007). Cardiac atrophy in women following bed rest. *J Appl Physiol*, 103(1):8–16.
- [26] Dorfmueller, P., Perros, F., Balabanian, K., and Humbert, M. (2003). Inflammation in pulmonary arterial hypertension. *Eur Respir J*, 22:358–363.
- [27] Edes, I., Kiss, E., Kitada, Y., Powers, F. M., Papp, J. G., Kranias, E. G., and Solaro, R. J. (1995). Effects of Levosimendan, a Cardiotonic Agent Targeted to Troponin C, on Cardiac Function and on Phosphorylation and Ca<sup>2+</sup> Sensitivity of Cardiac Myofibrils and Sarcoplasmic Reticulum in Guinea Pig Heart. *Circ Res*, 77(1):107–113.
- [28] Esposito, F., Mathieu-Costello, O., Shabetai, R., Wagner, P. D., and Richardson, R. S. (2010). Limited maximal exercise capacity in patients with chronic heart failure: partitioning the contributors. *J Am Coll Cardiol*, 55(18):1945–54.
- [29] Fabiato, A. and Fabiato, F. (1978). Effects of pH on the myofilaments and the sarcoplasmic reticulum of skinned cells from cardiac and skeletal muscles. *J Physiol*, 276:233–55.
- [30] Fadel, E., Mercier, O., Mussot, S., Leroy-Ladurie, F., Cerrina, J., Chapelier, A., Simonneau, G., and Dartevelle, P. (2010). Long-term outcome of double-lung and heart-lung transplantation for pulmonary hypertension: a comparative retrospective study of 219 patients. *Eur J Cardiothorac Surg*, 38(3):277–84.
- [31] Filusch, A., Ewert, R., Altesellmeier, M., Zugck, C., Hetzer, R., Borst, M. M., Katus, H. a., and Meyer, F. J. (2011). Respiratory muscle dysfunction in congestive heart failure - The role of pulmonary hypertension. *Int J Cardiol*, 150(2):182–185.
- [32] Fukuda, N., Wu, Y., Farman, G., Irving, T. C., and Granzier, H. (2005). Titin-based modulation of active tension and interfilament lattice spacing in skinned rat cardiac muscle. *Pflugers Archiv - Eur J Physiol*, 449(5):449–57.
- [33] Galie, N., Corris, P. a., Frost, A., Girgis, R. E., Granton, J., Jing, Z. C., Klepetko, W., McGoan, M. D., McLaughlin, V. V., Preston, I. R., Rubin, L. J., Sandoval, J., Seeger, W., and Keogh, A. (2013). Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*, 62(25 Suppl):D60–72.

- [34] Galiè, N., Hoepfer, M. M., Humbert, M., Torbicki, A., Vachiery, J.-L., Barbera, J. a., Beghetti, M., Corris, P., Gaine, S., Gibbs, J. S., Gomez-Sanchez, M. a., Jondeau, G., Klepetko, W., Opitz, C., Peacock, A., Rubin, L., Zellweger, M., and Simonneau, G. (2009). Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*, 34(6):1219–63.
- [35] Gan, C. T.-J., Lankhaar, J.-W., Marcus, J. T., Westerhof, N., Marques, K. M., Bronzwaer, J. G. F., Boonstra, A., Postmus, P. E., and Vonk-Noordegraaf, A. (2006). Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. *Am J Physiol Heart Circ Physiol*, 290(4):H1528–33.
- [36] Geiger, P. C., Cody, M. J., Macken, R. L., Bayrd, M. E., and Sieck, G. C. (2001). Effect of unilateral denervation on maximum specific force in rat diaphragm muscle fibers. *J Appl Physiol*, 90(4):1196–1204.
- [37] Geiger, P. C., Cody, M. J., Macken, R. L., and Sieck, G. C. (2000). Maximum specific force depends on myosin heavy chain content in rat diaphragm muscle fibers. *J Appl Physiol*, 89(2):695–703.
- [38] Gibson, G. J., Whitelaw, W., Siafakas, N., Supinski, G. S., Fitting, J. W., Bellemare, F., Loring, S. H., Troyer, A. D., and Grassino, A. E. (2002). ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med*, 166(4):518–624.
- [39] Gomes-Marcondes, M. C. C. and Tisdale, M. J. (2002). Induction of protein catabolism and the ubiquitin-proteasome pathway by mild oxidative stress. *Cancer Lett*, 180(1):69–74.
- [40] Gorman, J. L., Liu, S. T. K., Slopack, D., Shariati, K., Hasane, A., Olenich, S., Olfert, I. M., and Haas, T. L. (2014). Angiotensin II evokes angiogenic signals within skeletal muscle through co-ordinated effects on skeletal myocytes and endothelial cells. *PLoS one*, 9(1):e85537.
- [41] Grünig, E., Ehlken, N., Ghofrani, A., Staehler, G., Meyer, F. J., Juenger, J., Opitz, C. F., Klose, H., Wilkens, H., Rosenkranz, S., Olschewski, H., and Halank, M. (2011). Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. *Respiration*, 81(5):394–401.
- [42] Grünig, E., Lichtblau, M., Ehlken, N., Ghofrani, H. a., Reichenberger, F., Staehler, G., Halank, M., Fischer, C., Seyfarth, H.-J., Klose, H., Meyer, A., Sorichter, S., Wilkens, H., Rosenkranz, S., Opitz, C., Leuchte, H., Karger, G., Speich, R., and Nagel, C. (2012). Safety and efficacy of exercise training in various forms of pulmonary hypertension. *Eur Respir J*, 40(1):84–92.
- [43] Gurudevan, S. V., Malouf, P. J., Auger, W. R., Waltman, T. J., Madani, M., Raisinhan, A. B., DeMaria, A. N., and Blanchard, D. G. (2007). Abnormal left ventricular diastolic filling in chronic thromboembolic pulmonary hypertension: true diastolic dysfunction or left ventricular underfilling? *J Am Coll Cardiol*, 49(12):1334–9.
- [44] Haddad, F., Doyle, R., Murphy, D. J., and Hunt, S. A. (2008a). Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation*, 117(13):1717–31.
- [45] Haddad, F., Hunt, S. A., Rosenthal, D. N., and Murphy, D. J. (2008b). Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation*, 117(11):1436–48.
- [46] Haeck, M. L. a., Höke, U., Marsan, N. A., Holman, E. R., Wolterbeek, R., Bax, J. J., Schalij, M. J., Vliegen, H. W., and Delgado, V. (2014). Impact of right ventricular dyssynchrony on left ventricular performance in patients with pulmonary hypertension. *Int J Cardiovasc Imaging*, 30(4):713–20.
- [47] Han, Y.-S., Geiger, P. C., Cody, M. J., Macken, R. L., and Sieck, G. C. (2003). ATP consumption rate per cross bridge depends on myosin heavy chain isoform. *J Appl Physiol*, 94(6):2188–96.
- [48] Handoko, M. L., de Man, F. S., Happe, C. M., Schalij, I., Musters, R. J., Westerhof, N., Postmus, P. E., Paulus, W. J., van der Laarse, W. J., and Vonk-Noordegraaf, A. (2009). Opposite effects of training in rats with stable and progressive pulmonary hypertension. *Circulation*, 120(1):42–49.
- [49] Handoko, M. L., Schalij, I., Kramer, K., Sebkhi, A., Postmus, P. E., van der Laarse, W. J., Paulus, W. J., and Vonk-Noordegraaf, A. (2008). A refined radio-telemetry technique to monitor right ventricle or pulmonary artery pressures in rats: a useful tool in pulmonary hypertension research. *Pflugers Archiv - Eur J Physiol*, 455(5):951–959.
- [50] Hardegree, E. L., Sachdev, A., Fenstad, E. R., Villarraga, H. R., Frantz, R. P., McGoon, M. D., Oh, J. K., Ammash, N. M., Connolly, H. M., Eidem, B. W., Pellikka, P. A., and Kane, G. C. (2013). Impaired Left Ventricular Mechanics in Pulmonary Arterial Hypertension: Identification of a Cohort at High Risk. *Circ Heart Fail*, 6:748–755.
- [51] Hardziyenka, M., Campian, M. E., Reesink, H. J., Surie, S., Bouma, B. J., Groenink, M., Klemens, C. A., Beekman, L., Remme, C. A., Bresser, P., and Tan, H. L. (2011a). Right ventricular failure following chronic

- 
- pressure overload is associated with reduction in left ventricular mass evidence for atrophic remodeling. *J Am Coll Cardiol*, 57(8):921–8.
- [52] Hardziyenka, M., Campian, M. E., Verkerk, A. O., Surie, S., van Ginneken, A. C. G., Hakim, S., Linnenbank, A. C., de Bruin-Bon, H. A. C. M. R., Beekman, L., van der Plas, M. N., Remme, C. A., van Veen, T. A. B., Bresser, P., de Bakker, J. M. T., and Tan, H. L. (2012). Electrophysiologic remodeling of the left ventricle in pressure overload-induced right ventricular failure. *J Am Coll Cardiol*, 59(24):2193–202.
- [53] Hardziyenka, M., Surie, S., de Groot, J. R., de Bruin-Bon, H. a. C. M. R., Knops, R. E., Rummelink, M., Yong, Z.-Y., Baan, J., Bouma, B. J., Bresser, P., and Tan, H. L. (2011b). Right ventricular pacing improves haemodynamics in right ventricular failure from pressure overload: an open observational proof-of-principle study in patients with chronic thromboembolic pulmonary hypertension. *Europace*, 13(12):1753–9.
- [54] Harvey, P. A. and Leinwand, L. A. (2011). The cell biology of disease: cellular mechanisms of cardiomyopathy. *J Cell Biol*, 194(3):355–65.
- [55] Hassoun, P. M., Mouthon, L., and Barbera, J. A. (2009). Inflammation, growth factors and pulmonary vascular remodeling. *J Am Coll Cardiol*, 54:S10–S19.
- [56] Hoeper, M. M., Pletz, M. W., Golpon, H., and Welte, T. (2007). Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J*, 29:944–950.
- [57] Holverda, S., Gan, C. T.-J., Marcus, J. T., Postmus, P. E., Boonstra, A., and Vonk-Noordegraaf, A. (2006). Impaired stroke volume response to exercise in pulmonary arterial hypertension. *J Am Coll Cardiol*, 47(8):1732–3.
- [58] Hooijman, P., Beishuizen, A., de Waard, M., Vermeijden, J., Steenvoorde, P., Bouwman, R., Lommen, W., van Hees, H. W., Dickhoff, C., van der Peet, D., Girbes, A., Jasper, J., Malik, F., Stienen, G. J., Hartemink, K. J., Paul, M. A., and Ottenheijm, C. A. (2014). Diaphragm Fiber Strength Is Reduced in Critically Ill Patients and Restored by a Troponin Activator. *Am J Respir Crit Care Med*, 7:863–865.
- [59] Hoppeler, H., Baum, O., Lurman, G., and Mueller, M. (2011). Molecular mechanisms of muscle plasticity with exercise. *Compr Physiol*, 1(3):1383–412.
- [60] Howell, S., Maarek, J.-M. I. M., Fournier, M., Sullivan, K., Zhan, W.-Z. Z., and Sieck, G. C. (1995). Congestive heart failure: differential adaptation of the diaphragm and latissimus dorsi. *J Appl Physiol*, 79(2):389–397.
- [61] Humbert, M., Sitbon, O., Chaouat, A., Bertocchi, M., Habib, G., Gressin, V., Yaïci, A., Weitzenblum, E., Corder, J.-F., Chabot, F., Dromer, C., Pison, C., Reynaud-Gaubert, M., Haloun, A., Laurent, M., Hachulla, E., Cottin, V., Degano, B., Jaïs, X., Montani, D., Souza, R., and Simonneau, G. (2010). Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation*, 122(2):156–63.
- [62] Ito, K., Nkakyama, M., Hasan, F., Xinhua, Y., Schneider, M. D., and Lorell, B. H. (2003). Contractile reserve and calcium regulation are depressed in myocytes from chronically unloaded hearts. *Circulation*, 107(8):1176–1182.
- [63] Jaijee, S., O'Rourke, R., Puranik, R., Slaughter, R., Strugnal, W., Celermajer, D., Kermeen, F., and O'Rourke, R. (2013). Right to left ventricular volume ratio: A novel marker of disease severity in chronic thromboembolic pulmonary hypertension. *IJC Heart & Vessels*, 1:17–21.
- [64] Jarvis, J. C., Mokrusch, T., Kwende, M. M., Sutherland, H., and Salmons, S. (1996). Fast-to-slow transformation in stimulated rat muscle. *Muscle Nerve*, 19(11):1469–1475.
- [65] Kabitz, H.-J., Bremer, H.-C., Schwoerer, A., Sonntag, F., Walterspacher, S., Walker, D. J., Ehlken, N., Staehler, G., Windisch, W., and Grünig, E. (2013). The Combination of Exercise and Respiratory Training Improves Respiratory Muscle Function in Pulmonary Hypertension. *Lung*, 192:321–328.
- [66] Kabitz, H.-J., Schwoerer, A., Bremer, H.-C., Sonntag, F., Walterspacher, S., Walker, D., Schaefer, V., Ehlken, N., Staehler, G., Halank, M., Klose, H., Ghofrani, H. A., Hoeper, M. M., Greunig, E., and Windisch, W. (2008). Impairment of respiratory muscle function in pulmonary hypertension. *Clinical Science*, 114:165–171.
- [67] Kamler, M., Herold, U., Piotrowski, J., Bartel, T., Teschler, H., and Jakob, H. (2004). Severe left ventricular failure after double lung transplantation: pathophysiology and management. *J Heart Lung Transplant*, 23(1):139–142.
- [68] Kasner, M., Westermann, D., Steendijk, P., Dröse, S., Poller, W., Schultheiss, H.-P., and Tschöpe, C. (2012). Left ventricular dysfunction induced by nonsevere idiopathic pulmonary arterial hypertension: a pressure-volume relationship study. *Am J Respir Crit Care Med*, 186(2):181–9.
- [69] Kerckhoffs, R. C. P., Omens, J., and McCulloch, A. D. (2012). A single strain-based growth law pre-

- dicts concentric and eccentric cardiac growth during pressure and volume overload. *Mechanics research communications*, 42:40–50.
- [70] Kooij, V., Saes, M., Jaquet, K., Zarella, R., Foster, D. B., Murphy, A. M., Dos Remedios, C., van der Velden, J., and Stienen, G. J. M. (2010). Effect of troponin I Ser23/24 phosphorylation on Ca<sup>2+</sup>-sensitivity in human myocardium depends on the phosphorylation background. *J Mol Cell Cardiol*, 48(5):954–63.
- [71] Kozàková, M., Malshi, E., Morizzo, C., Pedri, S., Santini, F., Biolo, G., Pagani, M., Palombo, C., and Kozakova, M. (2011). Impact of prolonged cardiac unloading on left ventricular mass and longitudinal myocardial performance: an experimental bed rest study in humans. *J Hypertens*, 29(1):137–143.
- [72] Kumagai, M., Kondo, T., Ohta, Y., and Ishihara, T. (2001). Size and composition changes in diaphragmatic fibers in rats exposed to chronic hypercapnia. *Chest*, 119:565–571.
- [73] Lai, Y. L., Lamm, W. J. E., and Hildebrandt, J. (1981). Ventilation during prolonged hypercapnia in the rat. *J Appl Physiol*, 51:78–83.
- [74] Lamberts, R. R., Vaessen, R. J., Westerhof, N., and Stienen, G. J. M. (2007). Right ventricular hypertrophy causes impairment of left ventricular diastolic function in the rat. *Basic Res Cardiol*, 102(1):19–27.
- [75] Levine, R. L., Williams, J. A., Stadtman, E. R., and Shacter, E. (1994). Carbonyl assays for determination of oxidatively modified proteins. *Methods Enzymol*, 233:346–357.
- [76] Levine, S., Nguyen, T., Kaiser, L. R., Rubinstein, N. A., Maislin, G., Gregory, C., Rome, L. C., Dudley, G. A., Sieck, G. C., and Shrager, J. B. (2003). Human diaphragm remodeling associated with chronic obstructive pulmonary disease: clinical implications. *Am J Respir Crit Care Med*, 168(6):706–713.
- [77] LeWinter, M. M. and Granzier, H. (2010). Cardiac titin: a multifunctional giant. *Circulation*, 121(19):2137–45.
- [78] Li, Y.-p., Chen, Y., John, J., Moylan, J., Jin, B., Mann, D. L., and Reid, M. B. (2005). TNF- $\alpha$  acts via p38 MAPK to stimulate expression of the ubiquitin ligase atrogin1 / MAFbx in skeletal muscle. *The FASEB Journal*, 19:362–370.
- [79] Llewellyn, M. E., Barretto, R. P. J., Delp, S. L., and Schnitzer, M. J. (2008). Minimally invasive high-speed imaging of sarcomere contractile dynamics in mice and humans. *Nature*, 454(7205):784–8.
- [80] Lumens, J., Blanchard, D. G., Arts, T., Mahmud, E., and Delhaas, T. (2010). Left ventricular underfilling and not septal bulging dominates abnormal left ventricular filling hemodynamics in chronic thromboembolic pulmonary hypertension. *Am J Physiol Heart Circ Physiol*, 299(4):H1083–91.
- [81] Mainguy, V., Maltais, F., Saey, D., Gagnon, P., Martel, S., Simon, M., and Provencher, S. (2010a). Effects of a rehabilitation program on skeletal muscle function in idiopathic pulmonary arterial hypertension. *J Cardiopulm Rehabil Prev*, 30(5):319–23.
- [82] Mainguy, V., Maltais, F. F., Saey, D., Gagnon, P., Martel, S., Simon, M., and Provencher, S. (2010b). Peripheral muscle dysfunction in idiopathic pulmonaryarterial hypertension. *Thorax*, 65(2):113–117.
- [83] Manders, E., Bogaard, H.-J., Handoko, M. L., van de Veerdonk, M. C., Keogh, A., Westerhof, N., Stienen, G. J. M., Dos Remedios, C. G., Humbert, M., Dorfmueller, P., Fadel, E., Guignabert, C., van der Velden, J., Vonk-Noordegraaf, A., de Man, F. S., and Ottenheijm, C. A. C. (2014a). Contractile dysfunction of left ventricular cardiomyocytes in patients with pulmonary arterial hypertension. *J Am Coll Cardiol*, 64(1):28–37.
- [84] Manders, E., Bonta, P. I., Kloek, J. J., Symersky, P., Westerhof, N., Stienen, G. J., Vonk-noordegraaf, A., de Man, F. S., and Ottenheijm, C. A. C. (2014b). Diaphragm Dysfunction In Pulmonary Arterial Hypertension Patients. *Am J Respir Crit Care Med*, 189:A6347.
- [85] Manders, E., de Man, F. S., Handoko, M. L., Westerhof, N., van Hees, H. W. H., Stienen, G. J. M., Vonk-Noordegraaf, A., and Ottenheijm, C. A. C. (2012). Diaphragm weakness in pulmonary arterial hypertension: role of sarcomeric dysfunction. *Am J Physiol Lung Cell Mol Physiol*, 303(12):L1070–L1078.
- [86] Manders, E., Ruiters, G., Bogaard, H.-J., Stienen, G. J. M., Vonk-Noordegraaf, A., de Man, F. S., and Ottenheijm, C. A. C. (2015). Quadriceps muscle fiber dysfunction in patients with pulmonary arterial hypertension. *Eur Respir J*, Accepted.
- [87] Manning, H. L. and Schwartzstein, R. M. (1995). Pathophysiology of dyspnea. *N Engl J Med*, 333:1547–1553.
- [88] Mantilla, C. B. and Sieck, G. C. (2003). Plasticity in respiratory motor control. Invited Review:Mechanisms underlying motor unit plasticity in the respiratory system. *J Appl Physiol*, 94:1230–1241.
- [89] Mantilla, C. B. and Sieck, G. C. (2013). Impact of diaphragm muscle fiber atrophy on neuromotor control. *Respir Physiol Neurobiol*, 189(2):411–8.

- 
- [90] Marco, E., Ramírez-Sarmiento, A. L., Coloma, A., Sartor, M., Comin-Colet, J., Vila, J., Enjuanes, C., Bruguera, J., Escalada, F., Gea, J., and Orozco-Levi, M. (2013). High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure: a prospective randomized trial. *Eur J Heart Fail*, 15(8):892–901.
- [91] Marcus, J. T., Gan, C. T.-J., Zwanenburg, J. J. M., Boonstra, A., Allaart, C. P., Götte, M. J. W., and Vonk-Noordegraaf, A. (2008). Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am Coll Cardiol*, 51(7):750–7.
- [92] Marcus, J. T., Vonk Noordegraaf, A., Roeleveld, R. J., Postmus, P. E., Heethaar, R. M., Van Rossum, A. C., and Boonstra, A. (2001). Impaired left ventricular filling due to right ventricular pressure overload in primary pulmonary hypertension: noninvasive monitoring using MRI. *Chest*, 119(6):1761–5.
- [93] Matuszczak, Y., Farid, M., Jones, J., Lansdowne, S., Smith, M. a., Taylor, A. a., and Reid, M. B. (2005). Effects of N-acetylcysteine on glutathione oxidation and fatigue during handgrip exercise. *Muscle & nerve*, 32(5):633–8.
- [94] Mauritz, G.-J., Vonk-Noordegraaf, A., Kind, T., Surie, S., Kloek, J. J., Bresser, P., Saouti, N., Bosboom, J., Westerhof, N., and Marcus, J. T. (2012). Pulmonary endarterectomy normalizes interventricular dyssynchrony and right ventricular systolic wall stress. *J Cardiovasc Magn Reson*, 14(1):5.
- [95] McArdle, W. D., Katch, F. I., and Katch, V. L. (2010). *Exercise Physiology: Nutrition, Energy, and Human Performance*. Lippincott Williams & Wilkins.
- [96] Mello, P. R., Guerra, G. M., Borile, S., Rondon, M. U., Alves, M. J., Negrão, C. E., Dal Lago, P., Mostarda, C., Irigoyen, M. C., and Consolim-Colombo, F. M. (2012). Inspiratory muscle training reduces sympathetic nervous activity and improves inspiratory muscle weakness and quality of life in patients with chronic heart failure: a clinical trial. *J Cardiopulm Rehabil Prev*, 32(5):255–61.
- [97] Mereles, D., Elkhen, N., Kreuzer, S., Ghofrani, S., Hoepfer, M. M., Halank, M., Meyer, F. J., Karger, G., Buss, J., Juenger, J., Holzapfel, N., Opitz, C., Winkler, J., Herth, F. F. J., Wilkens, H., Katus, H. A., Olschewski, H., Grunig, E., Ehlken, N., and Grünig, E. (2006). Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*, 114(14):1482–1489.
- [98] Meyer, F. J., Borst, M. M., Zugck, C., Kirschke, A., Schellberg, D., Kübler, W., and Haass, M. (2001). Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. *Circulation*, 103(17):2153–2158.
- [99] Meyer, F. J., Lossnitzer, D., Kristen, A. V., Schoene, A. M., Kübler, W., Katus, H. A., and Borst, M. M. (2005). Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. *Eur Respir J*, 25(1):125–130.
- [100] Mone, S. M., Sanders, S. P., and Colan, S. D. (1996). Control Mechanisms for Physiological Hypertrophy of Pregnancy. *Circulation*, 94(4):667–672.
- [101] Moylan, J. S. and Reid, M. B. (2007). Oxidative stress, chronic disease, and muscle wasting. *Muscle Nerve*, 35(4):411–429.
- [102] Naeije, R. (2005). Breathing more with weaker respiratory muscles in pulmonary arterial hypertension. *Eur Respir J*, 25(1):6–8.
- [103] Nagel, C., Prange, F., Guth, S., Herb, J., Ehlken, N., Fischer, C., Reichenberger, F., Rosenkranz, S., Seyfarth, H.-J., Mayer, E., Halank, M., and Grünig, E. (2012). Exercise training improves exercise capacity and quality of life in patients with inoperable or residual chronic thromboembolic pulmonary hypertension. *PLoS one*, 7(7):e41603.
- [104] Oakley, B. R., Kirsch, D. R., and Morris, N. R. (1980). A simplified ultrasensitive silver stain for detecting proteins in polyacrylamide gels. *Anal Biochem*, 105(2):361–363.
- [105] Ottenheijm, C. A. C., Heunks, L. M. A., Sieck, G. C., Zhan, W.-Z., Jansen, S. M., Degens, H., de Bo, T., and Dekhuijzen, P. N. R. (2005). Diaphragm dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 172:200–205.
- [106] Ottenheijm, C. A. C., van Hees, H. W. H., Heunks, L. M. A., and Granzier, H. (2011). Titin-based mechanosensing and signaling: role in diaphragm atrophy during unloading? *Am J Physiol Lung Cell Mol Physiol*, 300(2):L161—L166.
- [107] Pasque, M. K., Trulock, E. P., Kaiser, L. R., and Cooper, J. D. (1991). Single-lung transplantation for pulmonary hypertension. Three-month hemodynamic follow-up. *Circulation*, 84(6):2275–9.
- [108] Perhonen, M. A., Franco, F., Lane, L. D., Buckley, J. C., Blomqvist, C. G., Zerwekh, J. E., Peshock,

- R. M., Weatherall, P. T., and Levine, B. D. (2001). Cardiac atrophy after bed rest and spaceflight. *J Appl Physiol*, 91(2):645–53.
- [109] Potus, F., Malenfant, S., Graydon, C., Mainguy, V., Tremblay, E., Breuils-Bonnet, S., Ribeiro, F., Porlier, A., Maltais, F., Bonnet, S., and Provencher, S. (2014). Impaired angiogenesis and peripheral muscle microcirculation loss contribute to exercise intolerance in pulmonary arterial hypertension. *Am J Respir Crit Care Med*, 190(3):318–28.
- [110] Provencher, S., Chemla, D., Hervé, P., Sitbon, O., Humbert, M., and Simonneau, G. (2006). Heart rate responses during the 6-minute walk test in pulmonary arterial hypertension. *Eur Respir J*, 27(1):114–20.
- [111] Pryor, W. A. and Squadrito, G. L. (1995). The chemistry of peroxynitrite: a product from the reaction of nitric oxide with superoxide. *Am J Physiol*, 268(5 Pt 1):L699—L722.
- [112] Quarck, R., Nawrot, T., Meyns, B., and Delcroix, M. (2009). C-reactive protein: a new predictor of adverse outcome in pulmonary arterial hypertension. *J Am Coll Cardiol*, 53(14):1211–8.
- [113] Rain, S., Bos, D. D. S. G., Handoko, M. L., Westerhof, N., Stienen, G., Ottenheijm, C., Goebel, M., Dorfmueller, P., Guignabert, C., Humbert, M., Bogaard, H.-J., Remedios, C. D., Saripalli, C., Hidalgo, C. G., Granzier, H. L., Vonk-Noordegraaf, A., van der Velden, J., and de Man, F. S. (2014a). Protein changes contributing to right ventricular cardiomyocyte diastolic dysfunction in pulmonary arterial hypertension. *J Am Heart Assoc*, 3(3):1–11.
- [114] Rain, S., Handoko, M. L., Vonk Noordegraaf, A., Bogaard, H. J., van der Velden, J., and de Man, F. S. (2014b). Pressure-overload-induced right heart failure. *Pflugers Archiv - Eur J Physiol*, 466:1055–1063.
- [115] Rain, S., Handoko, M. L., Westerhof, N., Stienen, G. J. M., Paulus, W. J., Ottenheijm, C. A. C., Marcus, J. T., Dorfmueller, P., Guignabert, C., Humbert, M., McDonald, P., Dos Remedios, C. G., Postmus, P. E., Vonk-Noordegraaf, A., van der Velden, J., de Man, F. S., Trip, P., Gan, C. T.-J., Dorfmueller, P., Macdonald, P., Saripalli, C., Hidalgo, C. G., and Granzier, H. L. (2013). Right ventricular diastolic impairment in patients with pulmonary arterial hypertension. *Circulation*, 128(18):2016–25.
- [116] Reid, M. B., Lännergren, J., and Westerblad, H. k. (2002). Respiratory and limb muscle weakness induced by tumor necrosis factor-alpha: involvement of muscle myofilaments. *Am J Respir Crit Care Med*, 166(4):479–84.
- [117] Ruiter, G., Ying Wong, Y., de Man, F. S., Louis Handoko, M., Jaspers, R. T., Postmus, P. E., Westerhof, N., Niessen, H. W. M., van der Laarse, W. J., and Vonk-Noordegraaf, A. (2013). Right ventricular oxygen supply parameters are decreased in human and experimental pulmonary hypertension. *J Heart Lung Transplant*, 32:231–240.
- [118] Russell, A. J., Hartman, J. J., Hinken, A. C., Muci, A. R., Kawas, R., Driscoll, L., Godinez, G., Lee, K. H., Marquez, D., Browne, W. F., Chen, M. M., Clarke, D., Collibee, S. E., Garard, M., Hansen, R., Jia, Z., Lu, P.-p., Rodriguez, H., Saikali, K. G., Schaletzky, J., Albertus, D. L., Claffin, D. R., Morgans, D. J., Morgan, B. P., and Malik, F. I. (2012). Activation of fast skeletal muscle troponin as a potential therapeutic approach for treating neuromuscular diseases. *Nature medicine*, 18(3):452–455.
- [119] Sachdev, A., Villarraga, H. R., Frantz, R. P., McGoon, M. D., Hsiao, J.-F., Maalouf, J. F., Ammash, N. M., McCully, R. B., Miller, F. a., Pellikka, P. a., Oh, J. K., and Kane, G. C. (2011). Right ventricular strain for prediction of survival in patients with pulmonary arterial hypertension. *Chest*, 139(6):1299–309.
- [120] Schwoerer, A. P., Neuber, C., Schmechel, A., Melnychenko, I., Mearini, G., Boknik, P., Kirchhefer, U., Schmitz, W., Ehmke, H., Eschenhagen, T., and El-Armouche, A. (2008). Mechanical unloading of the rat heart involves marked changes in the protein kinase-phosphatase balance. *J Mol Cell Cardiol*, 45(6):846–52.
- [121] Sieck, G. C. and Prakash, Y. S. (1997). Cross-bridge kinetics in respiratory muscles. *Eur Resp J*, 10:2147–2158.
- [122] Sieck, G. C., Zhan, W. Z., Han, Y. S., and Prakash, Y. S. (2007). Effect of denervation on ATP consumption rate of diaphragm muscle fibers. *J Appl Physiol*, 103:858–866.
- [123] Smith, M. A. and Reid, M. B. (2006). Redox modulation of contractile function in respiratory and limb skeletal muscle. *Respir Physiol Neurobiol*, 151(2-3):229–241.
- [124] Soon, E., Holmes, A. M., Treacy, C. M., Doughty, N. J., Southgate, L., Machado, R. D., Trembath, R. C., Jennings, S., Barker, L., Nicklin, P., Walker, C., Budd, D. C., Pepke-Zaba, J., and Morrell, N. W. (2010). Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension. *Circulation*, 122(9):920–7.
- [125] Stadtman, E. R. and Levine, R. L. (2003). Free radical-mediated oxidation of free amino acids and amino acid residues in proteins. *Amino Acids*, 25(3-4):207–218.
- [126] Stienen, G. J., Kiers, J. L., Bottinelli, R., and Reggiani, C. (1996). Myofibrillar ATPase activity in



- 
- skinned human skeletal muscle fibres: fibre type and temperature dependence. *J Physiol*, 493:299–307.
- [127] Sun, X. G., Hansen, J. E., Oudiz, R. J., and Wasserman, K. (2001). Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation*, 104:429–435.
- [128] Thistlethwaite, P. A., Kaneko, K., Madani, M. M., and Jamieson, S. W. (2008). Technique and outcomes of pulmonary endarterectomy surgery. *Ann Thorac Cardiovasc Surg*, 14(5):274–82.
- [129] Tonelli, A. R., Plana, J. C., Heresi, G. A., and Dweik, R. A. (2012). Prevalence and prognostic value of left ventricular diastolic dysfunction in idiopathic and heritable pulmonary arterial hypertension. *Chest*, 141(6):1457–65.
- [130] Toyooka, S., Kusano, K. F., Goto, K., Masaomi, Y., Oto, T., Sano, Y., Fuke, S., Okazaki, M., Ohe, T., Kasahara, S., Sano, S., and Date, H. (2009). Right but not left ventricular function recovers early after living-donor lobar lung transplantation in patients with pulmonary arterial hypertension. *J Thorac Cardiovasc Surg*, 138(1):222–226.
- [131] Trappe, S., Trappe, T., Gallagher, P., Harber, M., Alkner, B., and Tesch, P. (2004). Human single muscle fiber function with 84 day bed-rest and resistance exercise. *J Physiol*, 557:501–513.
- [132] Trappe, S., Williamson, D., Godard, M., Porter, D., Rowden, G., and Costill, D. (2000). Effect of resistance training on single muscle fiber contractile function in older men. *J Appl Physiol*, 89(1):143–52.
- [133] Trip, P., Kind, T., van de Veerdonk, M. C., Marcus, J. T., de Man, F. S., Westerhof, N., and Vonk-Noordegraaf, A. (2013). Accurate assessment of load-independent right ventricular systolic function in patients with pulmonary hypertension. *J Heart Lung Transplant*, 32(1):50–5.
- [134] Udaka, J., Ohmori, S., Terui, T., Ohtsuki, I., Ishiwata, S., Kurihara, S., and Fukuda, N. (2008). Disuse-induced preferential loss of the giant protein titin depresses muscle performance via abnormal sarcomeric organization. *J Gen Physiol*, 131(1):33–41.
- [135] van de Veerdonk, M. C., Kind, T., Marcus, J. T., Mauritz, G.-J., Heymans, M. W., Bogaard, H.-J., Boonstra, A., Marques, K. M. J., Westerhof, N., and Vonk-Noordegraaf, A. (2011). Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol*, 58(24):2511–9.
- [136] van der Velden, J., Merkus, D., de Beer, V., Hamdani, N., Linke, W. a., Boontje, N. M., Stienen, G. J. M., and Duncker, D. J. (2011). Transmural heterogeneity of myofilament function and sarcomeric protein phosphorylation in remodeled myocardium of pigs with a recent myocardial infarction. *Frontiers in Physiology*, 2:83.
- [137] van der Velden, J., Papp, Z., Zaremba, R., Boontje, N. M., de Jong, J. W., Owen, V. J., Burton, P. B. J., Goldmann, P., Jaquet, K., and Stienen, G. J. M. (2003). Increased Ca<sup>2+</sup>-sensitivity of the contractile apparatus in end-stage human heart failure results from altered phosphorylation of contractile proteins. *Cardiovasc Res*, 57(1):37–47.
- [138] van Dijk, S. J., Paalberends, E. R., Najafi, A., Michels, M., Sadayappan, S., Carrier, L., Boontje, N. M., Kuster, D. W. D., van Slegtenhorst, M., Dooijes, D., dos Remedios, C., ten Cate, F. J., Stienen, G. J. M., and van der Velden, J. (2012). Contractile dysfunction irrespective of the mutant protein in human hypertrophic cardiomyopathy with normal systolic function. *Circ Heart Fail*, 5(1):36–46.
- [139] van Hees, H. W. H., Dekhuijzen, P. N. R., and Heunks, L. M. A. (2009). Levosimendan Enhances Force Generation of Diaphragm Muscle from Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*, 179:41–47.
- [140] van Hees, H. W. H., Li, Y.-P., Ottenheijm, C. A. C., Hin, B., Pigmans, C. J. C., Linkels, M., Dekhuijzen, P. N. R., and Heunks, L. M. A. (2008). Proteasome inhibition improves diaphragm function in congestive heart failure rats. *Am J Physiol Lung Cell Mol Physiol*, 294(6):L1260–L1268.
- [141] van Hees, H. W. H., Schellekens, W.-J. M., Andrade Acuña, G. L., Linkels, M., Hafmans, T., Ottenheijm, C. A. C., Granzier, H. L., Scheffer, G.-J., van der Hoeven, J. G., Dekhuijzen, P. N. R., and Heunks, L. M. A. (2012). Titin and diaphragm dysfunction in mechanically ventilated rats. *Intensive Care Med*, 38(4):702–709.
- [142] van Hees, H. W. H., van der Heijden, H. F. M., Ottenheijm, C. A. C., Heunks, L. M. A., Pigmans, C. J. C., Verheugt, F. W. A., Brouwer, R. M. H. J., Dekhuijzen, P. N. R., and Hees, H. W. H. V. (2007). Diaphragm single-fiber weakness and loss of myosin in congestive heart failure rats. *Am J Physiol Heart Circ Physiol*, 293(1):H819—H828.
- [143] van Wolferen, S. A., Marcus, J. T., Boonstra, A., Marques, K. M. J., Bronzwaer, J. G. F., Spreuwenberg, M. D., Postmus, P. E., and Vonk-Noordegraaf, A. (2007). Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *Eur Heart J*, 28(10):1250–7.

- [144] Verbelen, T., Van Cromphaut, S., Rega, F., and Meyns, B. (2012). Acute left ventricular failure after bilateral lung transplantation for idiopathic pulmonary arterial hypertension. *J Thorac Cardiovasc Surg*, 145(1):1–3.
- [145] Vescovo, G., Ceconi, C., Bernocchie, P., Ferrari, R., Carraro, U., Ambrosio, G. B., and Libera, L. D. (1998). Skeletal muscle myosin heavy chain expression in rats with monocrotaline induced cardiac hypertrophy and failure. Relation to blood flow and degree of muscle atrophy. *Cardiovasc Res*, 39:233–241.
- [146] Vizza, C. D., Lynch, J. P., Ochoa, L. L., Richardson, G., and Trulock, E. P. (1998). Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest*, 113(3):576–83.
- [147] Vonk-Noordegraaf, A., Haddad, F., Chin, K. M., Forfia, P. R., Kawut, S. M., Lumens, J., Naeije, R., Newman, J., Oudiz, R. J., Provencher, S., Torbicki, A., Voelkel, N. F., and Hassoun, P. M. (2013). Right Heart Adaptation to Pulmonary Arterial Hypertension. *J Am Coll Cardiol*, 62(25):D22–D33.
- [148] Weiner, R. B. and Baggish, A. L. (2012). Exercise-induced cardiac remodeling. *Prog Cardiovasc Dis*, 54(5):380–6.
- [149] Welvaart, W. N., Paul, M. A., Stienen, G. J. M., van Hees, H. W. H., Loer, S. A., Bouwman, R., Niessen, H., de Man, F. S., Witt, C. C., Granzier, H., Vonk-Noordegraaf, A., and Ottenheijm, C. A. C. (2011a). Selective diaphragm muscle weakness after contractile inactivity during thoracic surgery. *Ann Surg*, 254(6):1044–1049.
- [150] Welvaart, W. N., Paul, M. a., van Hees, H. W. H., Stienen, G. J. M., Niessen, J. W. M., de Man, F. S., Sieck, G. C., Vonk-Noordegraaf, A., and Ottenheijm, C. a. C. (2011b). Diaphragm muscle fiber function and structure in humans with hemidiaphragm paralysis. *Am J Physiol Lung Cell Mol Physiol*, 301(2):L228–35.
- [151] Widmaier, E. P., Raff, H., and Strang, K. T. (2008). *Vander's Human Physiology - Mechanisms of Body Function*. McGraw-Hill, 11th editi edition.
- [152] Wüst, R. C. I., Myers, D. S., Stones, R., Benoist, D., Robinson, P. a., Boyle, J. P., Peers, C., White, E., and Rossiter, H. B. (2012). Regional skeletal muscle remodeling and mitochondrial dysfunction in right ventricular heart failure. *Am J Physiol Heart Circ Physiol*, 302(2):H402–11.
- [153] Xie, G. Y., Lin, C. S., Preston, H. M., Taylor, C. G., Kearney, K., Sapin, P. M., and Smith, M. D. (1998). Assessment of left ventricular diastolic function after single lung transplantation in patients with severe pulmonary hypertension. *Chest*, 114(2):477–81.
- [154] Yasunobu, Y., Oudiz, R. J., Sun, X. G., Hansen, J. E., and Wasserman, K. (2005). End-tidal {PCO<sub>2</sub>} abnormality and exercise limitations in patients with primary pulmonary hypertension. *Chest*, 127:1637–1646.
- [155] Yoshida, T., Galvez, S., Tiwari, S., Rezk, B. M., Semprun-Prieto, L., Higashi, Y., Sukhanov, S., Yablonka-Reuveni, Z., and Delafontaine, P. (2013). Angiotensin II inhibits satellite cell proliferation and prevents skeletal muscle regeneration. *J Biol Chem*, 288(33):23823–32.
- [156] Zafzir, B. (2013). Exercise training and rehabilitation in pulmonary arterial hypertension: rationale and current data evaluation. *J Cardiopulm Rehabil Prev*, 33(5):263–73.
- [157] Zhu, X., Heunks, L. M. A., Versteeg, E. M. M., van der Heijden, H. F. M., Ennen, L., van Kuppevelt, T. H., Vina, J., and Dekhuijzen, P. N. R. (2005). Hypoxia-induced dysfunction of rat diaphragm: role of peroxynitrite. *Am J Physiol Lung Cell Mol Physiol*, 288(1):L16—L26.



# Dankwoord

Na ruim 4 jaar zijn er natuurlijk veel mensen die een bedankje verdienen. Nu ben ik nogal kort en bondig van stof, dus ook in dit laatste stukje zal dat niet anders zijn. Dat neemt niet weg dat ik iedereen heel erg dankbaar ben voor hun bijdrage aan het voltooien van mijn boekje.

Als eerste mijn promotie team: Promotoren Prof. Anton Vonk-Noordegraaf en Prof. Ger Stienen, en co-promotoren Coen en Frances. Met zo'n uitgebreid team moest het ook wel goedkomen. De combinatie van fysiologie (experimenteel) en longziekten (klinisch) was af en toe moeilijk samen te brengen in de artikelen, maar dat is uiteindelijk toch elke keer weer gelukt en heeft mooie publicaties opgeleverd. Bedankt voor al jullie bijdrages.

Coen en Frances, ook jullie waren het onderling niet altijd eens, maar het was fijn dat ik dan degene was die de knoop zelf mocht doorhakken. Coen, jouw tomeloze enthousiasme over onderzoek en alles wat daarbij komt kijken was heel fijn. Jij was meestal enthousiaster over mijn data dan ikzelf en daarmee stak je mij ook een beetje aan. Frances, jij lette er altijd goed op dat ook het klinische publiek de resultaten op waarde kon schatten, dat heeft er zeker toe geleid dat de artikelen in mooie tijdschriften terecht zijn gekomen.

De leescommissie, Peter Bonta (dank voor het includeren van de CTEPH-patiënten), de overige leden Robert Naeije, Peter Wijkstra en Vanessa van Empel, bedankt voor de bereidheid om mijn proefschrift op wetenschappelijke waarde te beoordelen.

De collega's bij longziekten, ook al zag ik sommige van jullie maar heel af en toe. Bij vragen, samenwerkingen en hulp kon ik altijd bij jullie terecht. Ook de AIO's bij de afdeling longziekte, sectie PH, bedankt voor de samenwerking en gezelligheid op congressen.

De skeletgroep, oftewel de harem van Coen: Josine, Pleuni, Wies, Sanne, Kim, Saskia, Barbara, Vaishali, Marloes en, voor lange tijd de enige andere man Constantijn. Josine, we begonnen met z'n tweeën en één opstelling, maar al snel werd de groep uitgebreid en kwamen er ook meer opstellingen. Die hadden af en toe (stiekem best vaak)

kuren, en het was dringen om te meten. Gelukkig was iedereen heel flexibel en bleef het desondanks altijd gezellig op het lab. Dank voor de interessante inhoudelijke discussie van de data, maar ook voor de onzin praat en interessante muziek keuzes op het lab. Het was gezellig om met jullie allemaal samen te werken! Wies, top dat jij naast me wilt staan als paranimf. Je brengt veel gezelligheid en gekheid op het lab.

My roommates, Rosalie, Silvia, Michiel, Barbara and the newby Marloes. In general we kept it pretty calm in our room. Nevertheless, there was always room for interesting or less relevant discussions on the differences between the French and the Dutch, the peculiar hobbies of Michiel or why the Dutch language makes no sense. Barbara, good luck with the second part of your PhD. Michiel, don't stress too much, you will finish your thesis in time and Silvia, good luck with your new job.

Alle overige collega's van de Fysiologie. Ik zal de gezelligheid van de TPO weekenden, de vrijdagmiddagborrels, afdelingsuitjes en sportieve uitdagingen zeker gaan missen. Het was ontzettend fijn en gezellig om bij de fysiologie te werken!

Heel fijn is ook het delen van kleine of grotere frustraties met vrienden. Aangezien een verassend groot aantal ook bezig is met promotie onderzoek, of het al heeft afgerond, is het fijn om te merken dat iedereen op alle verschillende locaties en onderwerpen tegen dezelfde hobbels aanloopt of motivatie dipjes heeft. De Movers, we doen onze naam steeds meer eer aan, aangezien de helft nu toch echt al niet meer in Nederland woont. Zelfs binnen Nederland wonen/woonden we erg verspreid, maar we vinden gelukkig toch nog steeds tijd om af en toe spelletjes te spelen, lekker te eten en te kamperen.

Ook mijn mede badmintonners verdienen een bedankje. Het was heerlijk om frustraties, mislukte experimenten of afwijzingen er weer lekker 's avonds uit te meppen. Dat heeft er zeker aan bijgedragen dat ik mijn stress niveau goed onder controle kon houden.

Papa en mama, Loes en Ruud, thuis is toch nog altijd Limburg, ook al kom ik daar niet meer zo vaak. Dank jullie wel dat jullie mij gewoon lekker me gang hebben laten gaan en er gewoon op vertrouwen dat ik zelf de goede beslissingen neem. Loes, heel fijn dat jij als sterke vrouw naast mij wilt staan als paranimf. Hopelijk straalt dat dan een beetje op mij af. Mijn schoonfamilie, Ruud, Sabine, Renske en Sander. Bedankt voor de interesse die jullie altijd hebben getoond in mijn onderzoek. En Sabine en mama, het was ook heel leuk dat jullie onderdeel waren van een van mijn onderzoeken. Zo heb jullie toch een beetje kunnen zien waar ik nu aan werk en hoe het er aan toegaat, bedankt!

Als laatste natuurlijk Jarno. Ik vind het heerlijk met jou samen in Utrecht, maar ik ben ook benieuwd waar we wellicht hierna naartoe zullen gaan. Super fijn dat jij mee wilt gaan, dan komt namelijk alles vanzelf wel goed. ♥

# Curriculum Vitae

Emmy Manders was born on April 15th 1985 in Maasbree, the Netherlands. After finishing her secondary school education from Stella Maris College in Meerssen in 2003, she started with the Bachelor program Biomedical Engineering at the Eindhoven University of Technology followed by a Master in Biomechanical Engineering at the Soft Tissue Biomechanics and Engineering department. Emmy's master thesis centered on the topic of the individual and combined role of deformation, ischemia and reperfusion on skeletal muscle damage development, using T2 weighted MRI combined with mathematical modeling.

After graduating in 2010, Emmy decided to start her PhD research at the Department of Physiology and Pulmonology at the VU University Medical Center under the supervision of prof. Anton Vonk-Noordegraaf and Prof. Ger Stienen. The research focusses on striated muscle dysfunction in patients with pulmonary arterial hypertension, of which the results are presented in this thesis.



# List of Publications

**Manders, E.**, Rain, S., Bogaard, H.J., Vonk-Noordegraaf, A., Ottenheijm, C.A.C., and de Man, F.S. (2015) Back to basic - The striated muscles in pulmonary arterial hypertension; adaptations beyond the right ventricle. *European Respiratory Journal*. Invited review, In revision.

**Manders, E.**, Bonta, P.I., Kloek, J.J., Symersky, P., Bogaard, H.J., Hooijman, P.E., Jasper, J.R., Malik, F.I., Stienen, G.J.M., Vonk-Noordegraaf, A., de Man, F.S., and Ottenheijm, C.A.C. (2015). Reduced diaphragm muscle contractility in patients with chronic thromboembolic pulmonary hypertension. *Thorax*. In revision

**Manders, E.**, Ruiter, G., Bogaard, H.J., Stienen, G.J.M., Vonk-Noordegraaf, A., de Man, F.S., and Ottenheijm, C.A.C. (2015). Quadriceps muscle fiber dysfunction in patients with pulmonary arterial hypertension. *European Respiratory Journal*. Accepted

Ruiter, G., **Manders, E.**, Happé, C.M., Schalijs, I., Groepenhoff, H., Howard, L.S., Wilkins, M.R., Bogaard, H.J., Westerhof, N., van der Laarse, W.J., de Man, F.S., and Vonk-Noordegraaf, A. (2015) Intravenous iron therapy in patients with idiopathic pulmonary arterial hypertension and iron deficiency. *Pulmonary Circulation*. Accepted

Hooijman, P.E., Beishuizen, A., Witt, C.C., de Waard, M.C., Girbes, A.R.J., Spoelstra - de Man, A.M.E., Niessen, H.W.M., **Manders, E.**, van Hees, H.W.H., van den Brom, C.E., Silderhuis, V., Lawlor, M.W., Labeit, S., Stienen, G.J.M., Hartemink, K.J., Paul, M.A., Heunks, L.M.A., Ottenheijm, C.A.C. (2015) Diaphragm muscle fiber weakness and ubiquitin-proteasome activation in critically ill patients. *American Journal of Respiratory and Critical Care Medicine*. Accepted

**Manders, E.**, Bogaard, H.J., Handoko, M.L., van de Veerdonk, M.C., Keogh, A., Westerhof, N., Stienen, G.J.M., Dos Remedios, C.G., Humbert, M., Dorfmueller, P., Fadel, E., Guignabert, C., van der Velden, J., Vonk-Noordegraaf, A., de Man, F.S., and Ottenheijm, C.A.C. (2014). Contractile dysfunction of left ventricular cardiomyocytes in



patients with pulmonary arterial hypertension. *Journal of the American College of Cardiology*, 64(1):28-37.

**Manders, E.**, de Man, F.S., Handoko, M.L., Westerhof, N., van Hees, H.W.H., Stienen, G.J.M., Vonk-Noordegraaf, A., and Ottenheijm, C.A.C. (2012). Diaphragm weakness in pulmonary arterial hypertension: role of sarcomeric dysfunction. *American journal of physiology. Lung cellular and molecular physiology*, 303(12):L1070-L1078.

Loerakker, S., **Manders, E.**, Strijkers, G.J., Nicolay, K., Baaijens, F.P.T., Bader, D.L., and Oomens, C.W.J. (2011). The effects of deformation, ischemia, and reperfusion on the development of muscle damage during prolonged loading. *Journal of applied physiology*, 111(4):1168-77.

Loerakker, S., Oomens, C.W.J., **Manders, E.**, Schakel, T., Bader, D.L., Baaijens, F.P.T., Nicolay, K., and Strijkers, G.J. (2011). Ischemia-reperfusion injury in rat skeletal muscle assessed with T2-weighted and dynamic contrast-enhanced MRI. *Magnetic resonance in Medicine*, 66(2):528-37.