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RESEARCH ARTICLE

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Association of residual pulmonary hypertension with survival after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension

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Abstract

This study investigated whether residual pulmonary hypertension (PH), defined as early postoperative mean pulmonary artery pressure (mPAP) of ≥30 mmHg, after undergoing pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH) was associated with long-term survival. All patients who underwent PEA for CTEPH at two Scandinavian centers were included in this study. Baseline characteristics and vital statuses were obtained from patient charts and national health-data registers. The patients were then categorized based on residual PH measured via right heart catheterization within 48 h after undergoing PEA. Crude and weighted flexible parametric survival models were used to estimate the association between residual PH and all-cause mortality and to quantify absolute survival differences. From 1992 to 2020, 444 patients underwent surgery. We excluded 6 patients who died on the day of surgery and 12 patients whose early postoperative pulmonary hemodynamic data was unavailable. Of the total study population ($n = 426$), 174 (41%) and 252 (59%) patients had an early postoperative mPAP <30 and ≥30 mmHg, respectively. After weighting, there was a significant association between residual PH and all-cause mortality (hazard ratio: 2.49; 95% confidence interval [CI]: 1.60–3.87), and the absolute survival difference between the groups at 10 and 20 years was −22% (95% CI: −32% to −12%) and−32% (95% CI: −47% to −18%), respectively. A strong and clinically relevant association of residual PH with long-term survival after PEA for CTEPH was found. After accounting for differences in baseline characteristics, the absolute survival difference at long-term follow-up was clinically meaningful and imply careful surveillance to improve clinical outcomes in these patients. Early postoperative right heart catheter

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measurements of mPAP seem to be helpful for prognostication following PEA for CTEPH.

KEYWORDS
epidemiology, long-term prognosis, surgery

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease that has a poor prognosis if left untreated.[1] Guidelines recommend surgical treatment for operable CTEPH using pulmonary endarterectomy (PEA).[2] Patients ineligible for surgery may be treated using balloon pulmonary angioplasty[3] or targeted medical therapy to improve symptoms.[4,5] Many patients with CTEPH who undergo PEA postoperatively experience symptomatic relief, enhanced functional status, and an improved hemodynamic profile, and are considered cured of pulmonary hypertension (PH).[6–8] However, residual or persistent PH after PEA for CTEPH is common,[4,9–11] and according to expert opinion, the prevalence of persistent PH after PEA is underestimated.[12] PH is currently defined hemodynamically as a mean pulmonary arterial pressure (mPAP) of >20 mmHg at rest via right heart catheterization (RHC).[13] To date, there is no consensus on the definition of persistent or residual PH after PEA, and there are no threshold values for this phenomenon.[9,10] Previous research has indicated conflicting results regarding the relationship between early postoperative pulmonary hemodynamics and long-term survival.[1,7,14–18] Interpretation of prior studies is complicated because differing criteria to define persistent or residual PH have been used. Moreover, the timing and modality for acquiring hemodynamic measurements varied among studies. It is unclear if very early invasive postoperative measurements of mPAP that were obtained while the patient was still in the intensive care unit are clinically helpful for assessing long-term prognosis after PEA for CTEPH. Therefore, we conducted a bi-national observational cohort study aiming to investigate whether residual PH, defined as early postoperative mPAP ≥30 mmHg, after PEA for CTEPH was associated with worse long-term survival.

1 | METHODS

1.1 | Study design

This observational cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.[19] Approval was acquired from the Swedish Ethical Review Authority, and the need for informed consent was waived (registration numbers 2018/1296−31 and 2020−03130). The Central Denmark Region approved the study according to the Danish Health Act paragraph 42, section 2.

1.2 | Study population and data sources

The study population comprised all patients who underwent PEA for CTEPH at two centers in Scandinavia: Karolinska University Hospital, Stockholm, Sweden (1992–2020) and Aarhus University Hospital, Aarhus, Denmark (1994–2020). The study population is as described in a previous study.[20]

In the Swedish cohort, baseline characteristics and vital statuses were obtained from patient charts and national health-data registries using Swedish personal identity numbers.[21,22] Baseline characteristics in the Danish cohort were obtained from patient charts and vital statuses were obtained for all patients through a search of the Danish Civil Registration System.[23] Patients who died on the day of the operation ($n = 6$) and those with missing information on early postoperative mPAP ($n = 12$) were excluded. Clinical results were previously published for subsets of the Danish[24,25] and Swedish[8] cohorts.

1.3 | Exposure—definition of early postoperative PH (residual PH)

The study exposure was early postoperative PH (residual PH) defined as mPAP ≥30 mmHg obtained from invasive measurements within 24–48 h of surgery. Patients with early postoperative mPAP <30 mmHg were used as the control (nonexposed) group. The rationale for using 30 mmHg as the cut-off value was in line with previous studies suggesting this as a clinically significant level of residual PH.[7]

1.4 | Outcomes

The primary outcome was all-cause mortality. Person−time in days was calculated from the date of surgery to the date of death or end of follow-up (May 6, 2021 in the

TABLE 1 Baseline characteristics in 426 patients who underwent pulmonary endarterectomy in Sweden and Denmark 1993–2020

Variable	Total population	Early postoperative mean PAP		*p* value	Missing data (%)
		<30 mmHg	≥30 mmHg		
Number of patients	426 (100)	174 (40.8)	252 (59.2)		
Center				0.804	0.0
Denmark	310 (72.8)	125 (71.8)	185 (73.4)		
Sweden	116 (27.2)	49 (28.2)	67 (26.6)		
Age (years), mean (*SD*)	60.6 (13.2)	60.0 (14.4)	61.0 (12.4)	0.462	0.0
Female sex	176 (41.3)	60 (34.5)	116 (46.0)	0.023	0.0
Body mass index (kg/m^2)				0.332	27.9
<18.5	4 (1.3)	1 (0.7)	3 (1.8)		
18.5–24.99	118 (38.4)	47 (34.6)	71 (41.5)		
25–29.99	117 (38.1)	59 (43.4)	58 (33.9)		
≥30	68 (22.1)	29 (21.3)	39 (22.8)		
Smoking status				0.152	0.2
Never	200 (47.1)	87 (50.0)	113 (45.0)		
Former	183 (43.1)	66 (37.9)	117 (46.6)		
Current	42 (9.9)	21 (12.1)	21 (8.4)		
COPD	30 (7.5)	14 (8.6)	16 (6.8)	0.618	6.6
Diabetes	11 (2.8)	4 (2.5)	7 (3.0)	1.000	6.6
Peripheral artery disease	7 (1.8)	2 (1.2)	5 (2.1)	0.786	6.6
Coagulopathy	58 (13.6)	31 (17.8)	27 (10.7)	0.050	0.0
Riskfactor for VTE	37 (8.7)	13 (7.5)	24 (9.6)	0.568	0.7
History of VTE	341 (80.2)	150 (86.2)	191 (76.1)	0.014	0.2
WHO class				<0.001	1.9
I–II	45 (10.8)	28 (16.3)	17 (6.9)		
III	303 (72.5)	130 (75.6)	173 (70.3)		
IV	70 (16.7)	14 (8.1)	56 (22.8)		
Poor mobility	6 (1.5)	4 (2.5)	2 (0.8)	0.376	6.6
6-min walk test distance (m), mean (*SD*)	357 (133)	394 (128)	330 (131)	<0.001	32.2
Home oxygen therapy	57 (14.2)	15 (9.0)	42 (17.9)	0.018	5.6
PDEi treatment	75 (17.9)	25 (14.7)	50 (20.1)	0.201	1.6
Mean PAP (mmHg), mean (*SD*)	47 (11)	43 (11)	50 (10)	<0.001	0.9
Cardiac index (L/min/m^2), mean (*SD*)	2.1 (0.5)	2.2 (0.6)	2.0 (0.5)	0.001	11.0
PCWP (mmHg), mean (*SD*)	10 (3.6)	9.8 (3.4)	11 (3.7)	0.039	15.7
PVR (dynes·s·cm^{-5}), mean (*SD*)	808 (403)	656 (291)	916 (437)	<0.001	6.6
Endarterectomy reported as complete	358 (84.0)	159 (91.4)	199 (79.0)	0.001	0.0

(Continues)

TABLE 1 (Continued)

Variable	Total population	Early postoperative mean PAP		*p* value	Missing data (%)
		<30 mmHg	≥30 mmHg		
Year of surgery				0.006	0.0
1992–2003	63 (14.8)	16 (9.2)	47 (18.7)		
2004–2011	163 (38.3)	63 (36.2)	100 (39.7)		
2012–2020	200 (46.9)	95 (54.6)	105 (41.7)		

Note: Numbers are *n* (%) unless otherwise noted.

Abbreviations: COPD, chronic obstructive pulmonary disease; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PDEi, phosphodiesterase inhibitors; PVR, pulmonary vascular resistance; *SD*, standard deviation.

Swedish cohort and November 16, 2020 or April 1, 2021, in the Danish cohort).

1.5 | Statistical methods

Baseline characteristics were described as frequencies and percentages for categorical variables and means and standard deviations (*SD*s) for continuous variables. Optimization-based weights[26] were estimated to balance the differences in baseline characteristics in the two groups using the R package WeightIt.[27] All variables reported in Table 1 were used to derive the weights. Balance was evaluated after weighting using standardized mean differences. An absolute standardized difference of <0.1 was considered an ideal balance.[28] In the weighted population, flexible parametric survival models were used to estimate survival and the absolute survival difference with a 95% confidence interval (CI) between the groups.[29] Flexible parametric survival models were used to estimate the association between early postoperative mPAP ≥30 mmHg and survival (with mPAP <30 mmHg as the reference category) expressed as the hazard ratio (HR) and 95% CI, before and after weighting.

1.6 | Missing data

Variables with missing data are shown in Table 1. There were no missing outcome data. In the weighted analyses, missing data were handled by constructing the weights so that the rates of missingness were balanced between the groups.[27]

2 | RESULTS

From 1992 to 2020, 444 patients underwent PEA for CTEPH at the two Scandinavian centers. We excluded 6 patients who died on the day of surgery and 12 patients with no information regarding early postoperative mPAP; the total study population comprised 426 patients. The number of operations conducted per year during the study period is indicated in Figure S1. Baseline characteristics are reported in Table 1. The mean age of the total study population was 60.6 (*SD* 13.2) years, and women accounted for 41%. There were 174 patients (41%) with an early postoperative mPAP <30 mmHg and 252 patients (59%) with an early postoperative mPAP of ≥30 mmHg. The distribution of early postoperative mPAP is indicated in Figure 1. The yearly proportion of patients with early postoperative mPAP ≥30 mmHg slightly decreased during the study period (Figure S2). Before weighting, there were differences in the baseline characteristics of the patients with early postoperative mPAP <30 mmHg and those with early postoperative mPAP ≥30 mmHg (Table 1). Patients with early postoperative mPAP ≥30 mmHg were mostly female, more symptomatic according to WHO class, had shorter 6-min walk distance, and were more often on home oxygen treatment, and to a greater extent treated with phosphodiesterase inhibitors before surgery. They also had higher preoperative mPAP and pulmonary vascular resistance (PVR), and lower cardiac index, as well as endarterectomy being less often reported as complete. After weighting, all baseline characteristics were well balanced across the groups (Table S1 and Figure S3).

2.1 | Early mortality

The unadjusted 30-day all-cause mortality was 1.7% (3/174) and 7.5% (19/252) in patients with early postoperative mPAP <30 mmHg and those with early postoperative mPAP ≥30 mmHg, respectively ($p = 0.008$). After weighting, the 30-day mortality was 2.4% versus 6.5% in patients with early postoperative mPAP <30 and ≥ 30 mmHg, respectively ($p = 0.095$).

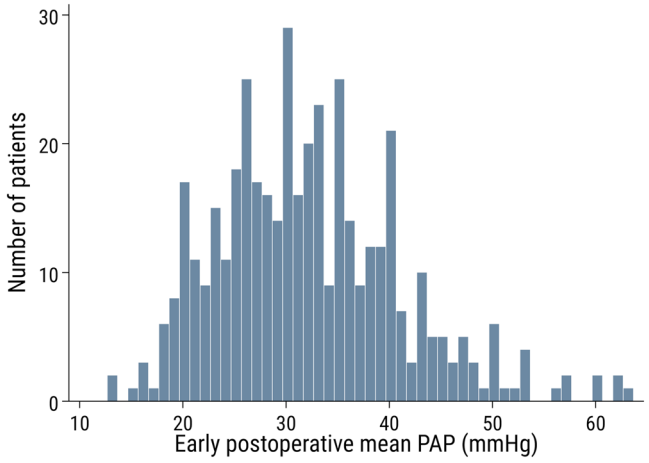

FIGURE 1 Distribution of early postoperative mean pulmonary artery pressure in 426 patients who underwent pulmonary endarterectomy. PAP, pulmonary artery pressure

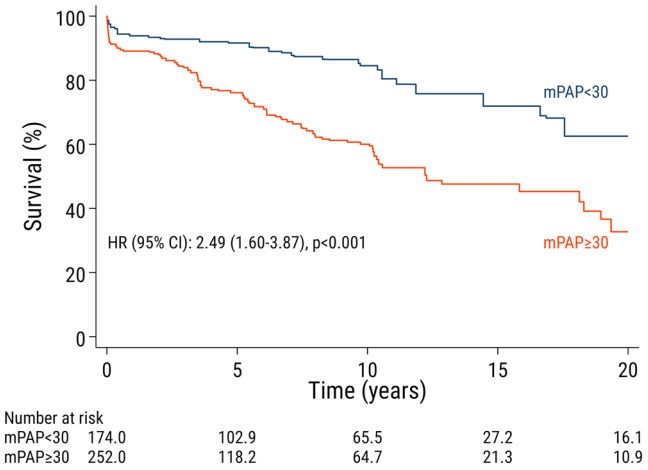

FIGURE 2 Kaplan–Meier estimated survival according to postoperative mean pulmonary artery pressure after pulmonary endarterectomy in the weighted population. Notably, the numbers of patients in the groups are not necessarily integers because of weighting. CI, confidence interval; HR, hazard ratio; mPAP, mean pulmonary artery pressure

2.2 | Overall survival

The mean and maximum follow-up times were 6.8 (*SD* 6.1) and 25.9 years, respectively. Before weighting, there was a significant difference in Kaplan–Meier estimated survival in patients with early postoperative mPAP <30 mmHg and those with early postoperative mPAP ≥30 mmHg (HR: 2.09; 95% CI: 1.42–3.07; $p < 0.001$) (Figure S4). The Kaplan–Meier estimated survival in the weighted population is shown in Figure 2. There was a significant difference in long-term survival in patients with early postoperative mPAP <30 mmHg and mPAP ≥30 mmHg (HR: 2.49; 95% CI: 1.60–3.87; $p < 0.001$). The 1-, 5-, 10-, 15-, and 20-year survival (95% CI) in the weighted population and absolute survival differences are reported in Table 2. Survival was significantly better in patients with early postoperative mPAP <30 mmHg compared with those with early postoperative mPAP ≥30 mmHg at all time points. After 10 years of follow-up, the survival was 81% (95% CI: 74%–88%), and 59% (95% CI: 52%–68%) in patients with early postoperative mPAP <30 and ≥30 mmHg, respectively. The absolute survival difference at 10 years was −22% (95% CI: −32% to −12%).

2.3 | Long-term survival conditional on survival beyond 30 days from surgery

The long-term survival in patients who survived the first 30 days after surgery is reported in Table 2. The results were similar to those of the total study population. Patients with early postoperative mPAP <30 mmHg had significantly better survival than patients with early postoperative mPAP ≥30 mmHg at all time points up to 20 years.

3 | DISCUSSION

A strong, significant, and clinically relevant association between very early postoperative mPAP ≥30 mmHg and long-term survival after PEA for CTEPH was found. This association remained after accounting for preoperative mPAP and other differences in baseline features and after excluding patients who did not survive beyond 30 d after surgery. The latter is essential because previous studies have provided solid evidence that patients with persistent or residual PH immediately following PEA have an increased risk of in-hospital death.[6,16] Our findings add to previous knowledge because they suggest that early mPAP ≥30 mmHg was relevant for prognosis also in patients who survived beyond the early postoperative phase.

Previous research has indicated conflicting results regarding the relationship between early postoperative pulmonary hemodynamics and long-term survival.[1,7,14–18] Direct comparisons of studies are difficult owing to the criteria for persistent or residual post-PEA PH varying across different studies, and also because measurements were obtained at various times after surgery (e.g., postoperative days 1–3, or 3–6 months postoperatively). Previous literature used different criteria to define persistent or residual PH, and some

TABLE 2 Survival in the total study population and according to early postoperative mean PAP, and the absolute survival difference after pulmonary endarterectomy

Time	Total population	Early postoperative mean PAP		Survival difference
		<30 mmHg	≥30 mmHg	
Overall survival				
1 year	91% (88%–94%)	95% (92%–97%)	88% (84%–92%)	−7.2% (−11% to −3.9%)
5 years	83% (80%–87%)	91% (87%–95%)	78% (73%–83%)	−12% (−18% to−6.9%)
10 years	68% (63%–74%)	81% (74%–88%)	59% (52%–68%)	−22% (−32% to −12%)
15 years	52% (46%–59%)	69% (60%–80%)	40% (33%–49%)	−29% (−42% to −16%)
20 years	39% (31%–48%)	58% (46%–73%)	25% (18%–36%)	−32% (−47% to −18%)
Conditional on 30-day survival				
1 year	97% (95%–99%)	98% (97%–100%)	96% (93%–98%)	−2.5% (−4.2% to −0.9%)
5 years	86% (82%–90%)	92% (88%–96%)	82% (76%–87%)	−10% (−16% to −5.0%)
10 years	73% (68%–79%)	84% (78%–90%)	65% (58%–73%)	−19% (−28% to −9.4%)
15 years	57% (51%–65%)	73% (63%–83%)	46% (38%–56%)	−27% (−39% to −14%)
20 years	41% (33%–51%)	59% (47%–75%)	28% (20%–39%)	−31% (−46% to −16%)

Note: Numbers are % and (95% confidence intervals) estimated from a flexible parametric survival model after weighting.

Abbreviation: PAP, pulmonary artery pressure.

used definitions based on mPAP,[1,7,15,17] while others used PVR,[16,18] or a combination of both.[14]

3.1 | High PVR post-PEA related to in-hospital mortality

Patients with residual PH after surgery, defined as high PVR, have been shown to have a higher risk of in-hospital mortality. Jamieson et al.[6] reported results from 1500 patients operated on in San Diego and found that patients with postoperative PVR >500 dyn·s·cm^{-5} had a mortality rate of 30%. Madani et al.[30] later reported similar results for mortality from the San Diego cohort of 2700 patients. High PVR and PH were related to increased postoperative mortality.

3.2 | Conflicting data—long-term outcomes not related to residual PH?

Freed et al.[15] included 314 patients who survived to discharge, and assessed the effect of residual PH defined as >30 mmHg at 3-month postoperatively on long-term survival after PEA. They found that patients with mPAP <30 mmHg at the 3-month follow-up had better exercise capacity, more improved symptoms, and fewer patients in this group were on PH-medication. There was no difference in survival between the two groups at the end of follow-up with a mean follow-up time of 4.2 years. Another study from the United Kingdom defined persistent PH at 3 months after PEA as mPAP of ≥25 mmHg and PVR of ≥240 dyn·s·cm^{-5}.[14] Of the 198 patients who survived PEA to discharge, 162 had a repeat right heart catheter at 3 months after surgery. Survival at 3 years after surgery was similar to the group with persistent PH compared with patients without persistent PH. In line with the results reported from the United Kingdom, a single-center cohort of 499 patients undergoing PEA between 1995 and 2014, residual PH was defined as mPAP ≥25 mmHg measured within 48 h of surgery and 34% had residual PH immediately postoperatively.[17] This group had a poorer prognosis; however, there was no significant difference in long-term survival between the groups after excluding in-hospital mortality.

3.3 | Residual PH—a prognostic marker for worse survival

In contrast, many studies reported a correlation between residual PH and worse survival.[1,7,18] The United Kingdom National Cohort included 880 patients between 1997 and 2012 and showed that mPAP ≥38 mmHg measured 3–6 months postoperatively correlated with worse long-term survival and higher risk of CTEPH-related death.[7] They found only a moderate correlation between days 1 and 3 to 6-month post-PEA mPAP. They concluded that 3–6-month mPAP was a better predictor of long-term

outcome than early postoperative pulmonary hemodynamics. Immediate postoperative PVR was found to be the strongest independent predictor of long-term survival or freedom from lung transplantation in 110 patients who underwent PEA in Vienna between 1994 and 2010.[18] The immediate postoperative period was defined as within 4 days of surgery. In the International prospective CTEPH-registry, 404 patients who underwent PEA were prospectively included in the registry between 2007 and 2009.[1] Residual postoperative PH was defined as mPAP ≥25 mmHg by RHC or systolic PAP ≥40 mmHg using echocardiography 2–3 days postoperatively and was significantly associated with an increased mortality at 3–5 years postoperatively.

There are many indications that pulmonary hemodynamics, pre-PEA, and post-PEA affect long-term patient outcomes and survival. The purpose of PEA is to clean the pulmonary arteries of obstruction (i.e., fibrotic material and scar tissue) and achieve a substantial improvement in pulmonary hemodynamics.[12] Possible explanatory mechanisms for very early mPAP ≥30 mmHg post-PEA could be related to incomplete endarterectomy or coexistent distal disease, but other factors may also be relevant in the very early postoperative phase. A meta-analysis indicated that residual PH was found in 25%, but this estimate must be interpreted in light of the absence of a generally accepted definition of residual PH post-PEA.[11]

The recent European Respiratory Society statement on CTEPH acknowledge that significant residual PH is a challenge to treat early postoperatively, and it is the most common cause of in-hospital mortality.[10] Short term mechanical circulatory support using extracorporeal membrane oxygenation may be necessary. Still, patients who develop symptoms after hospital discharge or during follow-up could be candidates for riociguat or balloon pulmonary angioplasty.[31]

3.4 | Future perspectives

Although the precise definition of residual PH following PEA for CTEPH remains debatable, the current study, together with prior reports, clearly indicate that patients with elevated mPAP early after surgery are at an increased risk of mortality compared to patients with lower mPAP. The possible benefits of using a fixed value (e.g., mPAP of 30 mmHg) for the definition of residual PH following PEA for CTEPH include that it is easily obtained and easy to use for decision making. However, one should bear in mind the drawbacks; the cut off value was arbitrarily chosen, and the optimal value is yet to be discovered. Moreover, if a patient falls just below the cut off, the prognosis is likely similar to another patient that is just above, and all measurements must be interpreted judiciously.

Although prior studies have consistently shown worse short-term outcomes in patients with residual PH, the results regarding long-term outcomes have been diverging. The current study findings were in line with two recent and important large studies; the United Kingdom National experience and the International prospective CTEPH-registry.[1,7] Taken together, these studies show that early postoperative pulmonary hemodynamics are of importance for long-term patient prognosis. Therefore, the message to clinicians caring for these patients must be to follow patients with residual PH closely to hopefully and possibly improve prognosis.

3.5 | Study limitations

The measurements of early mPAP were not obtained according to a standardized study protocol; they were obtained from patient charts and there was likely variability in timing and procedure. Also, information on the use of vasoactive medication and patient fluid status was unavailable. There was no information regarding several important factors that affect the long-term prognosis, including targeted medication, balloon pulmonary angioplasty, or anticoagulation strategy. Because the study period spanned over approximately 30 years, possible alterations in diagnosis, referral patterns, patient care, including perioperative management, medical treatment, and other factors could not be fully accounted for.

In conclusion, a strong and clinically relevant association of residual PH with long-term survival after PEA for CTEPH was detected. Our findings suggest that early mPAP ≥30 mmHg is relevant for prognosis, and the survival difference at long-term follow-up is clinically meaningful and warrants careful surveillance to improve clinical outcomes in these patients. Early postoperative right heart catheter measurements of mPAP in the intensive care unit seem helpful for prognostication following PEA for CTEPH.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Janica Kallonen, Kasper Korsholm, Søren Mellemkjær and Ulrik Sartipy: conceived and designed the

research. **Janica Kallonen, Kasper Korsholm, and Ulrik Sartipy**: acquired the data. **Janica Kallonen and Ulrik Sartipy**: performed statistical analyzes. **Janica Kallonen, Kasper Korsholm, Fredrik Bredin, Matthias Corbascio, Mads Jønsson Andersen, Lars Bo Ilkjær, Søren Mellemkjær, and Ulrik Sartipy**: contributed to the interpretation of data. **Janica Kallonen and Ulrik Sartipy**: drafted the manuscript. **Janica Kallonen, Kasper Korsholm, Fredrik Bredin, Matthias Corbascio, Mads Jønsson Andersen, Lars Bo Ilkjær, Søren Mellemkjær, and Ulrik Sartipy**: made critical revision of the manuscript for key intellectual content and have seen and approved the final version. **Ulrik Sartipy**: is the guarantor.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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