Exercise Training to Improve Outcomes in CHD

What we know, what we don't

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CINCYACHD

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Alfred

- 21-year-old man with D-TGA
- Arterial switch → ostial left coronary occlusion
- Identified early post surgery; did well until age 16 years
- He developed typical angina, + ischemia
- Underwent CABG, LIMA to LAD
- He was asymptomatic, but sedentary and obese

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Alfred

And guess what?

Alfred started exercising regularly.

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Alfred

He lost weight.

He felt better.

He loved it.

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Alfred

And then he developed bilateral inguinal hernias - likely related to exercise.

Surgical hernia repair was uneventful.

But he had stopped exercising.

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Exercise can be harmful. And for many decades, exercise restriction was standard.

But there is now consensus that exercise is beneficial in CHD, and encouraging exercise is our default.

Some reluctance persists in the form of '***Exercise, but.... Syndrome***'

What data support our dramatic shift?

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What are we talking about?

Physical activity: any bodily movement produced by skeletal muscles that requires energy expenditure.

Exercise: activity requiring physical effort, carried out to sustain or improve health and fitness.

https://en.wikipedia.org/wiki/Gustav_Zander

https://www.who.int/news-room/fact-sheets/detail/physical-activity

https://www.dailymail.co.uk/femail/article-3404801/Inside-Victorian-gym-Vintage-photos-dressed-men-women-testing-bizarre-contraptions-inspired-today-s-exercise-machines.html

Our focus

Aerobic exercise since it most directly relates to cardiovascular function, health, and disease.

But other forms of exercise may provide substantial benefit.

www.nia.nih.gov/health/infographics/benefits-4-types-exercise

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Exercise training varies

- Encouragement / counseling (not ‘training’)
- Exercise prescription (not ‘training’)
- Aerobic, many approaches
- Cardiac rehabilitation
- Inspiratory muscle
- Lower extremity muscle
- Flexibility (poster presented yesterday by Dr. Hansen)

Sources of evidence

- Anecdotal
- Observational data on physical activity
- Single arm interventions
- **Randomized trials**

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Cochrane Review

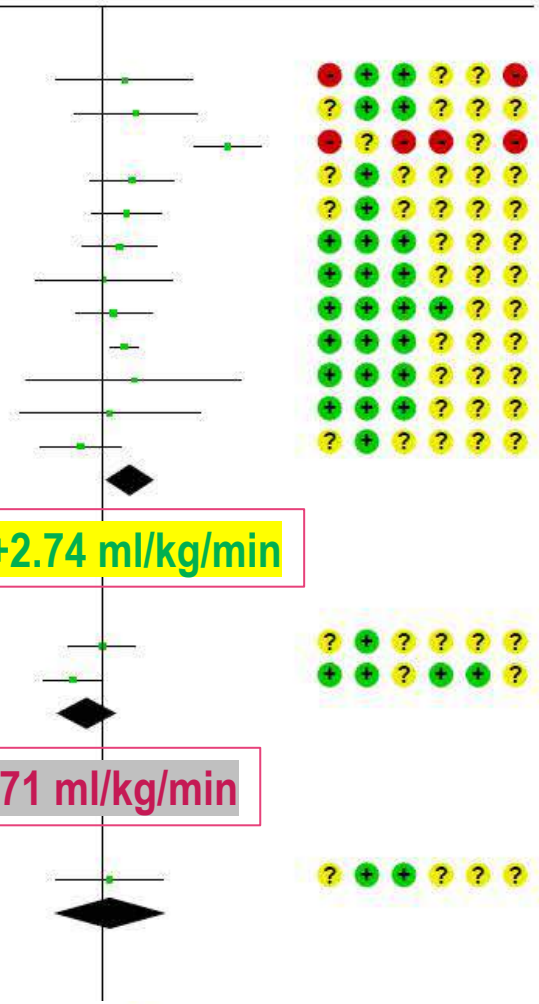
Physical activity interventions for people with CHD

- 15 RCTs with 924 participants
- 5 pediatric (n = 500); 10 adult (n = 424)
- Median intervention length = 12 weeks (IQR 12 to 26)
- 3 types of intervention
  - Physical activity promotion
  - Exercise training
  - Inspiratory muscle training

Williams CA, Wadey C, Pieles G, Stuart G, Taylor RS, Long L. Physical activity interventions for people with congenital heart disease. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD013400. DOI: 10.1002/14651858.CD013400.pub2. Accessed 24 February 2023.

Physical activity interventions for people with congenital heart disease - Williams, CA - 2020 | Cochrane Library

Study or Subgroup	Physical activity Mean [mL/kg/min]	SD [mL/kg/min]	Total	No activity (usual care) Mean [mL/kg/min]	SD [mL/kg/min]	Total	Weight	Mean Difference IV, Random, 95% CI [mL/kg/min]	Risk of Bias A B C D E F
1.1.1 Exercise training									
Therrien 2003	24.3	8.2	9	22.1	6.5	8	4.8%	2.20 [-4.80 , 9.20]	- + + ? ? -
Moalla 2006	33	6.2	10	29.6	7.2	8	5.4%	3.40 [-2.90 , 9.70]	? + + ? ? ?
Madhavi 2011	43.84	10.33	51	30.99	7.96	61	8.1%	12.85 [9.38 , 16.32]	- ? - - ? -
Winter 2012	29	7	24	26	8	22	7.2%	3.00 [-1.36 , 7.36]	? + ? ? ? ?
Westhoff-Bleck 2013	25.9	6.1	19	23.5	5.3	21	8.0%	2.40 [-1.16 , 5.96]	? + ? ? ? ?
Duppen 2015	35.9	7.4	43	34.2	8.6	30	7.8%	1.70 [-2.09 , 5.49]	+ + + ? ? ?
Avila 2016	28.6	7.1	13	28.5	6.01	4	4.8%	0.10 [-6.94 , 7.14]	+ + + ? ? ?
Sandberg 2018	25.1	6.16	13	24.03	3.33	10	7.6%	1.07 [-2.86 , 5.00]	+ + + + ? ?
Opotowsky 2018	1	1.5	13	-1.2	2.3	15	9.9%	2.20 [0.78 , 3.62]	+ + + ? ? ?
Novakovic 2018 (1)	26.5	12.5	9	23.3	8.5	5	2.7%	3.20 [-7.85 , 14.25]	+ + + ? ? ?
Novakovic 2018 (2)	24	6.2	9	23.3	8.5	4	3.5%	0.70 [-8.56 , 9.96]	+ + + ? ? ?
van Dissel 2019	25.4	6.6	17	27.7	5.6	17	7.4%	-2.30 [-6.41 , 1.81]	? + ? ? ? ?
Subtotal (95% CI)			**230**			**205**	**77.3%**	**2.74 [0.36 , 5.12]**	
Heterogeneity: Tau² = 10.92; Chi² = 40.79, df = 11 (P < 0.0001); I² = 73%									
Test for overall effect: Z = 2.26 (P = 0.02)									
1.1.2 Physical activity promotion									
Morrison 2013	37.4	8.8	62	37.5	8.6	39	8.1%	-0.10 [-3.58 , 3.38]	? + ? ? ? ?
Klausen 2016	43.2	9.7	81	46.3	10.1	77	8.5%	-3.10 [-6.19 , -0.01]	+ + ? + + ?
Subtotal (95% CI)			**143**			**116**	**16.6%**	**-1.71 [-4.64 , 1.22]**	
Heterogeneity: Tau² = 1.68; Chi² = 1.60, df = 1 (P = 0.21); I² = 37%									
Test for overall effect: Z = 1.14 (P = 0.25)									
1.1.3 Inspiratory muscle training									
Fritz 2020	24	8.3	18	23.3	9.1	20	6.1%	0.70 [-4.83 , 6.23]	? + + ? ? ?
Subtotal (95% CI)			**18**			**20**	**6.1%**	**0.70 [-4.83 , 6.23]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.25 (P = 0.80)									



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Is change in peak VO_2 a surrogate for outcomes in CHD?

Peak VO_2 is associated with the likelihood of adverse outcomes in many types of CHD, both in children and adults.

A couple studies suggest change in peak VO_2 is associated with change in likelihood of adverse outcomes.

No data exist to support that the effect of a given intervention on peak VO_2 is reliably associated with the effect of the intervention on outcomes.

Is that just because we don't have enough data?

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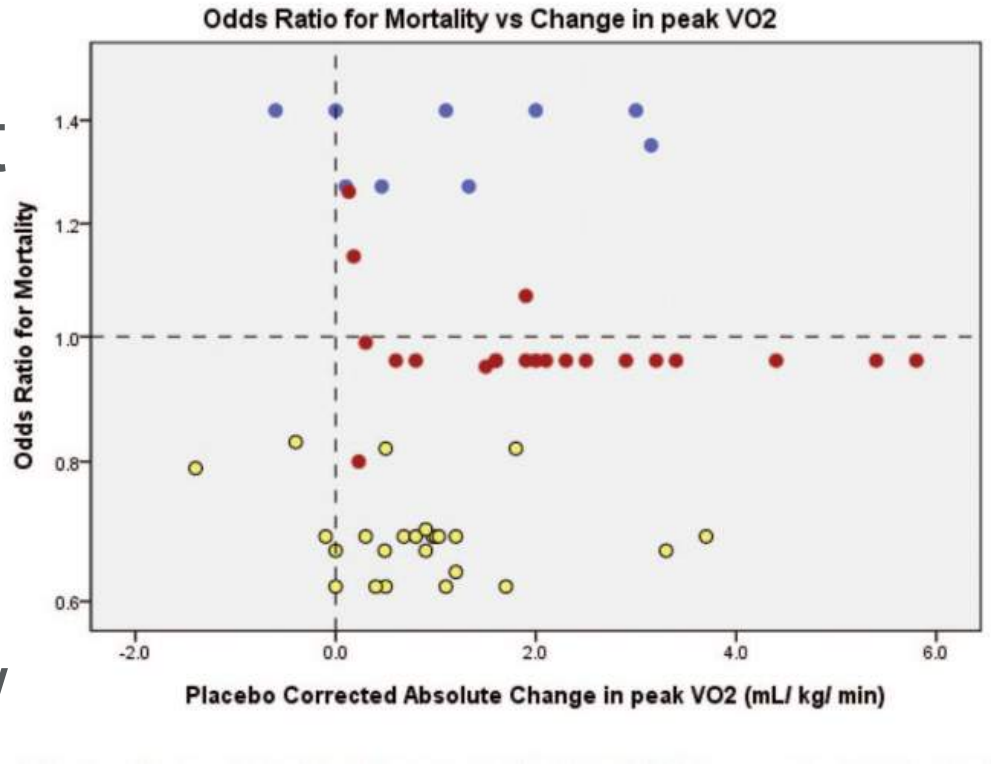
Is change in peak VO_2 a surrogate for outcomes in systolic heart failure?

Some interventions improve exercise performance, yet trials show no benefit

Others that provide benefit (eg β blockers) do not increase pVO_2

Overall, no consistent relationship between ΔpVO_2 and effect on mortality



Wessler, Benjamin S., et al. "Drug and Device Effects on Peak Oxygen Consumption, 6 Minute Walk Distance, and Natriuretic Peptides as Predictors of Therapeutic Effects on Mortality in Patients with Heart Failure and Reduced Ejection Fraction." *Circulation: Heart Failure* (2011).

Wolfel EE. Curr Heart Fail Rep. 2006 Jun;3(2):81-8.Exercise testing with concurrent beta-blocker usage: is it useful? What do we learn?

Witte KK, et al. Eur J Heart Fail. 2005 Jun;7(4):612-7. The effects of long-term beta-blockade on the ventilatory responses to exercise in chronic heart failure.

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Why might a patient be interested in exercise training?

- a) Social benefits of exercise / sports
- b) Feel better (symptomatic, self-esteem, psychological)
- c) Be able to participate more fully in more activities
- d) It is fun
- e) ↑ peak VO_2 and other measures of exercise response
- f) Better vascular function
- g) Better cardiac function
- h) Decrease the probability of specific complications
- i) Live longer

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Yes, I feel great. But my peak VO_2 is 2.74 ml/kg/min too low.

What About Exercise Training & Quality Of Life In CHD?

Author	n	Type of intervention	Questionnaire	Domain	Intervention vs. control at follow up	Effect
Duppen 2015	73	Exercise training	SF-36 (8 domains)	Physical functioning*	94.6 (10.9) 95.0 (8.5) P = 0.71	=
Madhavi 2011	112	Exercise training	SF-36 +	SF36 total score	23.3 (13.2) 11.3 (14.3) P < 0.001	↑
Klausen 2016	158	Phys activity promotion	Danish Paediatric QoL +	Generic, others	NR	=
Opotowsky 2018	28	Exercise training	MLHFQ -	MLHFQ	20.1 (11.4) 27.7 (10.9) P = 0.13	=
Sandberg 2018	23	Exercise training	EQ5D VAS +	EQ5D VAS	76.2 (15.2) 76.3 (20.7) P = 0.31	=
Novakovic 2018	14	Exercise training (Interval)	SF36 +	Physical component*	86.7 (40.2) 101.0 (16.6) P > 0.05	=
Novakovic 2018	13	Exercise training (Continuous)	SF36 +	Physical component*	103 (5.2) 101.0 (16.6) P > 0.05	=
Westhoff-Bleck 2013	40	Exercise training	KCCQ +	KCCQ	NR	=
Winter 2012	46	Exercise training	SF-36 +	Physical component*	P = 0.20	=
			ConHD-TAAQOL +	Symptom*	85 (10.79) 83 (10.47) P = 0.31	=

*Other components reported, all same qualitative result

Some Consistent (Worrisome) Findings

Modest effect size.

No appreciable benefit in how patients feel.

Adherence is problematic – even in brief, well-resourced studies.

Unclear sustained benefit.

1) *How do we get patients to want to exercise and to sustain an exercise habit?*
2) *Can we personalize exercise to pathophysiology for greater effect?*

How do we get patients to want to exercise and to sustain an exercise habit?

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

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Choir singing improves respiratory muscle strength and quality of life in patients with structural heart disease – HeartChoir: a randomised clinical trial

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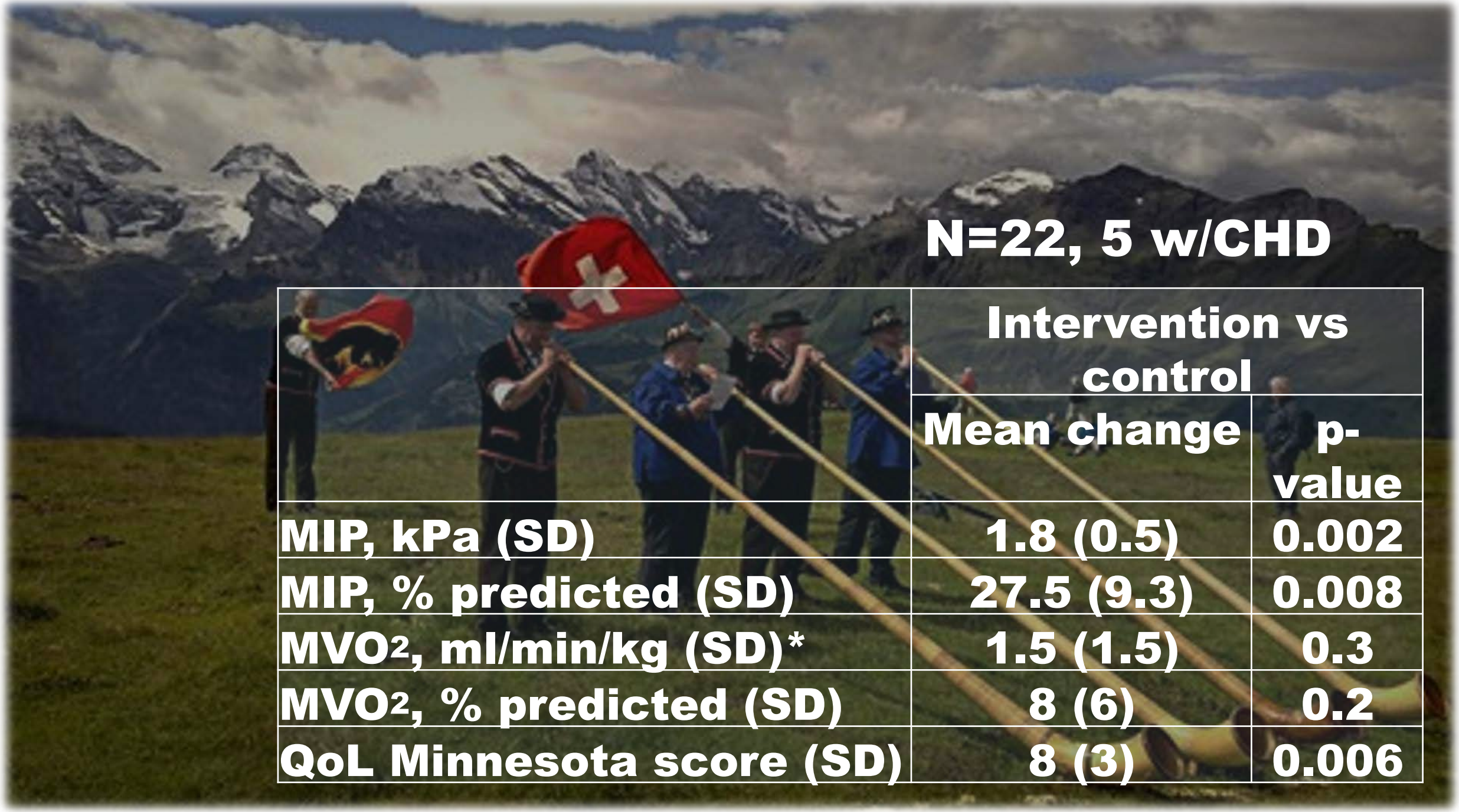

N=22, 5 w/CHD

	Intervention vs control	
	Mean change	p-value
MIP, kPa (SD)	1.8 (0.5)	0.002
MIP, % predicted (SD)	27.5 (9.3)	0.008
MVO_2, ml/min/kg (SD)*	1.5 (1.5)	0.3
MVO_2, % predicted (SD)	8 (6)	0.2
QoL Minnesota score (SD)	8 (3)	0.006

Can we personalize exercise to pathophysiology for greater effect?

Studies including children only:										
Jacobsen	2018	Cohort	13	0	Aerobic + resistance	–	12	3–4	60	Unsupervised, on television
Sutherland (home)	2018	Randomised trial	11	0	Aerobic + resistance	65–85% HR pk VO2	8	2	60	Unsupervised
Sutherland (hospital)	2018	Randomised trial	6	0	Aerobic + resistance	65–85% HR pk VO2	8	2	60	Supervised
Wittekind	2018	Cohort	10	0	Aerobic + resistance	70–80% of HRR	12	2	60	Supervised
Hedlund	2017	Cohort with controls	30	25	Aerobic training	–	12	2	45	Supervised
Laohachai	2017	Cohort	23	0	IMT	30% of MIP	6	7	30	Unsupervised
Longmuir	2013	Randomised trial	30	0	Aerobic + resistance	–	52	7	10–15	Unsupervised
Opocher	2005	Cohort	10	0	Aerobic training	50–70% of HR at pk VO2	32	2	30–45	Unsupervised
Studies including adults only:										
Fritz	2019	Randomised controlled trial	42	22	IMT	Adjusted individually	26	7	3 sets with 10–30 repetitions	Unsupervised
Wu	2018	Cohort	12	0	IMT	40% of MIP	12	5	30	Unsupervised
Cordina	2012	Cohort with controls	6	5	High-weight resistance training → on calf muscles.	–	20	3	60	Supervised
Lichtman	2008	Case study	1	0	Aerobic + resistance	19/20 on Borg scale	–	–	–	Supervised
Studies inc										
Ait Ali										
Duppen9										
Brassarc										
Minamis										
Balfour										

Peak VO_2 increased significantly in 56% of the studies (0% declined)

Average +1.72 ml/kg/min (+6.3%)

Adverse event reported in 4 studies - likely unrelated to training

Scheffers LE, vd Berg LEM, Ismailova G, Dulfer K, Takkenberg JJM, Helbing WA, Physical exercise training in patients with a Fontan circulation: A systematic review, *European Journal of Preventive Cardiology*, 2021.

What we know

Being sedentary is bad.

Some exercise is good. More is usually better.

Exercise is usually safe.

Exercise training increases exercise capacity.

Cardiac rehabilitation is effective in specific situations.

Few people sustain regular exercise.

There are specific obstacles to feeling comfortable exercising.

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Open questions

What types of exercise are best?

Are some types of exercise harmful or is anything better than nothing?

Does exercise early in life provide long term developmental gains?

How can we sustain short-term gains?

Does exercise training improve outcomes?

So where does that leave us?

- Start **early**, normalize physical activity and exercise
- **Recommend** exercise again & again & again
- Understand **context**: obstacles and motivations
- Individualized **support** (eg, speak w/ PE teacher)
- Informed **options** (eg, cardiac rehab, pickleball)
- Enroll in **research** for better understanding

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Thank you

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Can we personalize exercise to pathophysiology for greater effect?

Supine

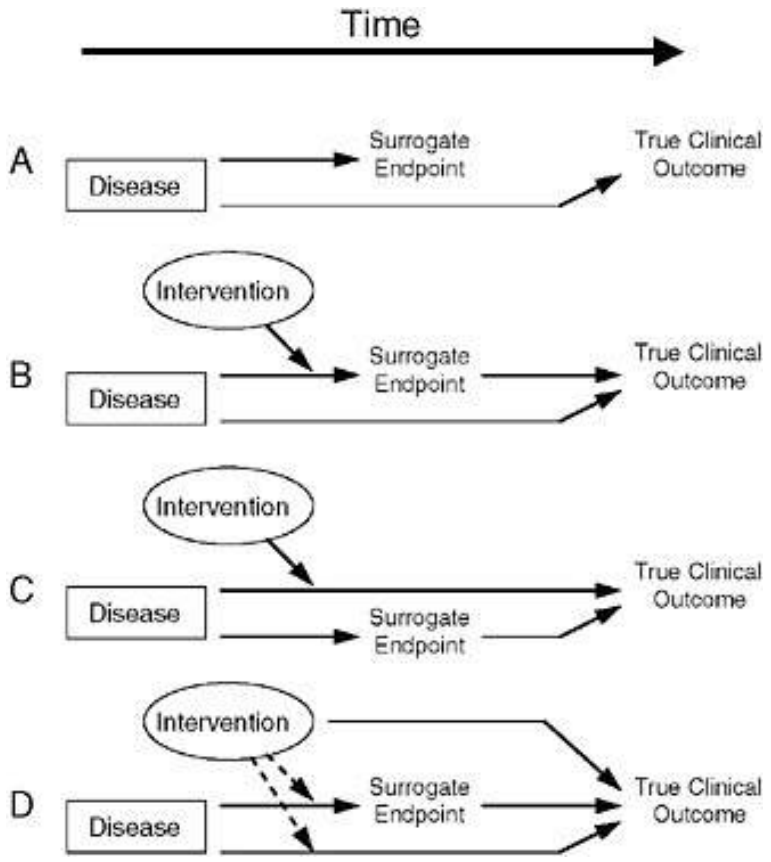
Upright

Position & Venous Distribution

L Rowell 1986

Surrogate endpoint ≠ strong correlate

- A surrogate endpoint should effectively substitute for a clinical outcome, meaning the effects of an intervention on a surrogate reliably predict the effect on the outcome
- A change in the surrogate due to the intervention must be tightly linked to a change in the likelihood of an outcome



Fleming, Thomas R., and John H. Powers. "Biomarkers and surrogate endpoints in clinical trials." *Statistics in medicine* 31.25 (2012): 2973-2984.; Fleming, Thomas R., and David L. DeMets. "Surrogate end points in clinical trials: are we being misled?." *Annals of internal medicine* 125.7 (1996): 605-613.

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