

Hemodynamic Response to Rapid Saline Infusion Compared with Exercise in Healthy Participants Aged 20–80 Years

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ABSTRACT

Background and Objective: Rapid saline infusion and exercise has been proposed as methods to unmask cardiovascular disease. However, the normal hemodynamic response to rapid saline infusion has not been compared to exercise nor is it known whether the responses are age-dependent.

We assessed the hemodynamic response to rapid saline infusion in healthy participants over a wide age-range and compared it to exercise in the same participants.

Methods and results: Fifty healthy participants (young <40 years, $n = 16$, middle-aged 40–59 years, $n = 15$, elderly 60–80 years, $n = 19$) underwent right heart catheterization at rest, during semisupine ergometer exercise at three exercise levels (25%, 50%, and 75% of peak $\dot{V}O_2$) and after rapid saline infusion (10 ml/kg at a rate of 150 ml/min). Rapid saline infusion significantly increased pulmonary capillary wedge pressure (PCWP) similarly across all age groups (Δ PCWP 6 ± 2 ; 7 ± 2 ; 6 ± 4 mmHg for the young, middle-aged and elderly respectively) with no correlation between age and Δ PCWP ($r = 0.05$; $p = 0.74$). However, there was a negative correlation between age and Δ stroke volume (SV) as elderly participants had a lower increase in SV following rapid saline infusion ($r = 0.44$; $p = 0.002$). On the contrary, exercise-induced significantly larger and age-dependent increases in PCWP ($r = 0.58$; $p < 0.0001$). Exercise also caused a larger increase in SV compared with rapid fluid loading ($p = 0.0003$).

Conclusion: Unlike exercise, rapid saline infusion caused an age-independent increase in PCWP in healthy adults. Suggesting that age-related impairments beyond passive stiffness have a greater impact on exercise-induced increase in PCWP.

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT01974557> (*J Cardiac Fail* 2019;25:902–910)

Key Words: Saline infusion, Exercise, Hemodynamics, Healthy.

Invasive hemodynamic assessment is an important tool in the diagnosis and management of cardiovascular disease due to the ability to simultaneously measure pressure and flow. It is used in the diagnosis and management of valvular heart disease, pericardial disease, congenital heart disease, pulmonary vascular disease and heart failure with reduced or preserved ejection fraction.¹ Many patients with early stages of heart disease will display normal hemodynamic values at rest but abnormal hemodynamic values when provoked with stressors such as exercise^{2,3} or rapid saline

infusion.^{4,5} Since rapid saline infusion is less complicated and more readily available despite being less physiologic and eliciting lesser hemodynamic response it is an attractive alternative to invasive hemodynamic exercise testing which requires a more complicated setup.^{6–8} A pulmonary capillary wedge pressure (PCWP) above 25 mmHg with exercise or more than 18 mmHg with rapid saline infusion is considered abnormal.^{5,9} It is well known that pulmonary pressures and ventricular filling pressures increase during exercise in healthy participants.^{3,10,11} The hemodynamic response to rapid saline infusion has been assessed in different cohorts but not over a wider age-range nor have they been compared to exercise in healthy individuals.^{4,6,9,12,13}

The HEMREX (The Effect of Age on the Hemodynamic Response During Rest and Exercise in Healthy Humans) study examined the hemodynamic response to exercise across different ages in healthy participants. The primary outcome measure was a composite of hemodynamic parameters. The study enrolled 62 healthy participants between 20 and 80 years of age in two Danish university hospitals.

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The study demonstrated that elderly participants had higher PCWP compared to younger participants during exercise.¹¹ It is unclear whether the same age-dependent response is seen with rapid saline infusion. Furthermore, it has been suggested that factors beyond impairments in left ventricular (LV) passive compliance determines the increases in PCWP during exercise.⁶ Therefore, we aimed to expand the HEMREX study to assess the hemodynamic response to rapid saline infusion and to compare the results to the exercise-induced hemodynamic response.

Methods

After approval of the initial HEMREX protocol, an amendment pertaining to rapid fluid loading was approved allowing 50 participants to be examined by both exercise and rapid fluid loading. Participants were eligible if they felt healthy, were non-smokers, had normal body mass index (BMI, 20–30 kg/m²), free from history of any acute or chronic pulmonary or cardiac disease; displayed structural normal heart on echocardiography performed 0–2 weeks before invasive test including normal LV ejection fraction (LVEF), normal chamber geometry, no valvular heart diseases (other than mild valvular stenosis or regurgitation); normal biochemistry (eGFR, HbA1c, NT-proBNP, TSH, Hgb, CRP and lipids); and cardiac exercise testing with normal ECG. All participants provided written and oral informed consent. The protocol was approved by the regional ethical committee (Capital Region of Denmark; H-2–2013–072) and registered on clinicaltrials.gov (NCT01974557).

Echocardiography

Echocardiography at rest, during exercise, pre- and post-saline infusion was performed according to guidelines¹² using an iE33 (Phillips Healthcare, Best, Netherlands) or a Vivid E9 (General Electric,) ultrasound system. Images were stored digitally for offline analysis using Phillips Xcelera software (version R4.1) or GE EchoPac (version 1.13).

Right Heart Catheterization

Right heart catheterization was performed using a triple lumen Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA). Using the Seldinger technique and guided by ultrasound the catheter was introduced through the internal jugular vein and advanced to the pulmonary artery (PA). Central venous pressure (CVP), systolic/diastolic/mean PA pressures (sPAP, dPAP, mPAP), and PCWP were assessed at end-expiration. Cardiac output (CO) was measured using thermodilution as the average of 3 measurements with <10% variance and was indexed to body surface area as cardiac index (CI). Brachial blood pressure was measured non-invasively by sphygmomanometry at baseline and at every 4 min until maximum workload was reached.

Calculations

Body surface area (BSA) was estimated using the Mosteller formula.¹³ Mean arterial pressure (MAP) was calculated as $\text{systolic pressure}/3 + (2 \times \text{diastolic pressure}/3)$. Pulmonary vascular resistance (PVR) was calculated as $(\text{mPAP} - \text{PCWP})/\text{CO}$. Systemic vascular resistance (SVR) was calculated as $80 \times (\text{MAP} - \text{CVP})/\text{CO}$. Stroke volume (SV) was calculated as $\text{CO}/\text{heart rate (HR)}$. Pulse pressures (PP) were calculated as $\text{systolic pressure} - \text{diastolic pressure}$. Systemic and pulmonary compliance (SAC and PAC) was calculated $\text{SV}/\text{systemic or pulmonary PP}$. Transmural filling pressure (TMP) an estimate of LV preload was calculated as the gradient between PCWP-CVP. Arterial and venous oxygen content was calculated as follows: Hemoglobin (g/dL) \times 1.34 (ml O₂/g hemoglobin) \times SatO₂. Arterio-venous difference (AVO₂) was calculated as arterial oxygen content – venous oxygen content.

Protocol and Interventions

Participants were examined in the non-fasting state, they were asked to refrain from consuming products containing caffeine on the day of the examination. After voiding, non-invasive and invasive equipment was placed (sphygmomanometer cuff, pulse oximeter, 5-lead ECG, sheath and Swan-Ganz catheter). After baseline data were acquired in the supine position with the legs resting flat on the surface, participants performed a multistage semi-supine cycle exercise at three 4 min exercise levels (25%, 50%, and 75% of peak VO₂). Participants were encouraged to maintain a pedaling speed of 60 rpm. Peak VO₂ was obtained from a standard cardiopulmonary exercise test performed less than 2 weeks prior to invasive exercise test. Workloads corresponding to 25%, 50% and 75% of peak VO₂ were used during the invasive exercise test. During the same procedure, after completing the exercise stage, participants rested for hemodynamic values to return to normal (>15 min) before acquiring re-baseline hemodynamics. Subsequently, isotonic saline was administered via sheath in the internal jugular vein at an infusion rate of 150 ml/min, until a total volume of 10 ml pr. kg bodyweight was infused. Immediately after completing the infusion, hemodynamics were reassessed.

Statistical Analyses

All data were formally tested for normality using Shapiro-Wilk tests, histograms, and normal probability plots. Results are reported as mean \pm SD for normally distributed variables, number (%) for categorical variables and median (Interquartile range) for non-normally distributed variables. Differences within the same individual were assessed by paired *t*-test. Between-group differences were tested by ANOVA for normally distributed data and Tukey's HSD (honestly significant difference) test was used to determine which group means differed. For non-normally distributed data, Wilcoxon rank sum test was used to assess for group

differences and to determine which group means differed. Pearson chi-square test was used in case of non-parametric data. Pearson's correlation coefficient was calculated to assess for correlation. All tests were two-sided, and a *p*-value of 0.05 was considered significant. All analyses were conducted using JMP version 13.2 (Wittington House, Buckinghamshire, Great Britain).

Results

Fifty healthy participants divided into three clinically meaningful groups (young < 40 years, *n* = 16; middle-aged 40–59 years, *n* = 15; elderly 60–80 years, *n* = 19). The three groups did not differ with regards to body size, gender, cardiac structure, arterio-venous difference or right ventricular function. There were clear age-related attenuations in peak VO₂, forced expiratory volume and diastolic function, Table 1. Younger participants had lower resting MAP, SVR and higher pulmonary compliance compared to the elderly participants. The middle-aged participants had higher MAP and SVR compared to the younger group and higher pulmonary vascular compliance in comparison to the elderly group. There was a tendency towards younger participants having larger resting SV (*p* = 0.07), Table 2.

Differences in Hemodynamic Response Between Exercise and Rapid Saline Infusion

Exercise caused larger increases in PCWP, CVP, TMP and an attenuated increase in cardiac index in elderly participants

compared to the younger age groups (*p* > 0.05 for all groups). This age-dependent attenuation of cardiac output reserve was not driven by age-dependent attenuations in SV reserve (*r* = –0.1; *p* = 0.54,) but by age-dependent attenuation in HR reserve (*r* = –0.42; *p* = 0.005). With exercise nine (16%) participants (3 middle-aged (20%) and 6 elderly (32%)) experienced a PCWP > 25 mmHg. There was no correlation between age and PCWP at rest (*r* = 0.04; *p* = 0.79), however, at peak exercise there was a positive correlation between PCWP and age (*r* = 0.53; *p* < 0.0001) as well as between ΔPCWP and age (*r* = 0.58; *p* < 0.0001). The correlation between age and PCWP was independent of peak VO₂.

Compared to rapid saline infusion, exercise caused far greater hemodynamic response except for CVP where rapid saline infusion caused a 50% larger increase.

Both pulmonary and systemic resistances decreased with exercise with no age-related differences. Systemic and pulmonary arterial compliances both increased slightly with exercise albeit only the increase in systemic arterial compliance was significant. The minimal changes in systemic and pulmonary arterial compliances with exercise were caused by large and relative parallel increases (approx. 50%) in SV and in systemic and pulmonary pulse pressures resulting in little or no changes in vascular arterial compliance (Fig. 1, panel a-f).

Hemodynamic Responses to Rapid Saline Infusion

Except from MAP and HR, rapid saline infusion induced significant increases in all systemic and pulmonary

Table 1. Baseline Characteristics

	Young (<40 years) 16 subjects	Middle-aged (40–59 years) 15 subjects	Elderly (60–80 years) 19 subjects	<i>p</i> -value
Mean age, years	31	49*	69*†	<0.0001
Female, n (%)	8 (50%)	4 (27%)	10 (53%)	0.27
Body surface area (m ²)	1.91±0.18	1.88±0.16	1.89±0.19	0.88
<i>Pulmonary function and biochemistry</i>				
FEV1 (l)	4.0 ± 0.8	3.3 ± 0.7	3.1 ± 0.7	0.002
FEV1/FVC (%)	81±7	76±10	76±11	0.32
Peak VO ₂ (ml/kg)	41.3 ± 7.9	33.8 ± 6.2	29.3 ± 7.0*	<0.0001
Hgb (g/dl)	14.3 ± 1.2	14.3 ± 1.0	14.3 ± 1.4	0.98
NT-proBNP (pmol/l)	9 (6–11)	8(6–14)	9(8–11)	0.64
eGFR (ml/min/1.73 m ²)	86±12	75±14	78±11	0.04
HbA1C (%)	33.2 ± 2.7	35.1 ± 3.0	36.3 ± 3.1	0.02
CRP (mg/l)	1(1–2)	1(1–3)	1(1–2)	0.91
<i>Echocardiography</i>				
LVEDD (mm)	47±6	46±9	44±6	0.59
LV ejection fraction (%)	59±6	61±6	65±7*	0.04
GLS (%)	19±4	20±2	20±3	0.54
LA volume index (mL/m ²)	22±7	20±10	24±9	0.39
Mitral E velocity (cm/s)	72±18	73±18	72±16	0.97
Mitral E/A ratio	1.9 ± 1.0	1.2 ± 0.3*	1.0 ± 0.3*	0.0004
Mitral e' velocity (cm/s)	12.5 ± 2.3	8.7 ± 2.0*	7.5 ± 1.8*	<0.0001
E/e' ratio	6 ± 2	9 ± 3*	10±2*	<0.0001

Values are mean ± SD, n (%) or median (Interquartile range).

FEV1, forced expiratory volume in 1 s; FVC, forced ventilator capacity; NT-proBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1C, glycosylated hemoglobin; CRP, c-reactive protein; LVEDD, Left ventricular end-diastolic diameter; LV, left ventricular; GLS, global longitudinal strain; LA, left atrial; TAPSE, tricuspid annular plane systolic excursion.

For between groups comparison **p*<0.05 vs < 40 years; †*p*<0.05 vs 40–59 years.

ANOVA was used to assess between group differences and Tukey HSD test was used to determine which group means differed for normally distributed data. Wilcoxon rank sum test was used to assess between group differences and which group means differed for non-normally distributed data. Pearson chi-square test was used to assess between group differences in case of non-parametric data.

Table 2. Hemodynamic Response to Exercise and Saline Infusion

	Young <40 years (16 subjects)				Middle-aged 40–59 years (15 subjects)				Elderly 60–80 years (19 subjects)				<i>p</i> -overall between groups		
	Baseline	Exercise	Re-baseline	saline	Baseline	Exercise	Re-baseline	saline	Baseline	Exercise	Re-baseline	saline	Baseline	Exercise	saline
HR (bpm)	62±13	145±17	66±11	67±10	66±9	138±14	70±12‡	69±10	63±8	129±16*	71±9‡‡	73±11	0.54	0.02	0.27
MAP (mmHg)	84±9	108±12	75±14‡	75±11	97±10*	123±21*	84±11‡	89±15*	99±9*	125±7*	94±13*	92±12*	<0.0001	0.008	0.0006
Cardiac output (L/min)	5.5 ± 1.1	18.8 ± 1.7	5.8 ± 1.0	8.5 ± 2.3	5.1 ± 0.9	17.1 ± 2.6	5.1 ± 0.9	6.9 ± 1.3*	5.0 ± 1.0	14.7 ± 2.8*†	5.4 ± 1.1‡	6.7 ± 1.3*	0.35	0.0002	0.007
Cardiac Index (L/min/m²)	2.9 ± 0.4	10±0.8‡	3.1 ± 0.5‡	4.5 ± 1.3	2.7 ± 0.3	9.1 ± 1.3	2.7 ± 0.3	3.7 ± 0.8	2.6 ± 0.4	7.9 ± 1.3*†	2.8 ± 0.5	3.5 ± 0.5*	0.2	<0.0001	0.01
A-V O₂ difference (ml/dl)	4.7 ± 0.6	12.1 ± 1.5	4.3 ± 0.6	4.5 ± 0.6	4.9 ± 0.8	12.6 ± 1.1	4.7 ± 0.4	4.8 ± 0.9	4.4 ± 0.6	12.5 ± 1.3	4.4 ± 1	4.5 ± 1.0	0.08	0.59	0.67
SV (ml)	94±27	128±15	89±20	127±33‡	79±20	127±21	75±17	101±17*	81±18	117±29	76±18	93±17*	0.14	0.33	0.0003
mPAP (mmHg)	12±3	23±5‡	13±4	18±4	14±3	31±12*	15±3	21±4	14±3	36±7*	16±5	21±5	0.08	0.0001	0.08
Mean PCWP (mmHg)	8 ± 2	13±4‡	8 ± 3	14±2	9 ± 3	19±10*	9 ± 3	15±4	8 ± 3	23±5*	9 ± 4	14±5	0.66	0.0002	0.66
DPG (mmHg)	0.9 ± 1.8	6.1 ± 0.8	1.6 ± 1.8	0.6 ± 3.1	1.7 ± 1.3	5.9 ± 0.8	2.7 ± 2.3	2.2 ± 2.7	1.1 ± 1.7	4.4 ± 0.7	2.9 ± 2.1‡	1.7 ± 2.0	0.45	0.24	0.23
PCWP > cut-off, n (%)	NA	0 (0%)	NA	0 (0%)	NA	3 (20%)	NA	4 (27%)	NA	6 (32%)	NA	2(11%)	NA	0.05	0.07
CVP (mmHg)	5 ± 2	7 ± 3‡	5 ± 2	12±5	5 ± 2	10±7	5 ± 2	13±4‡	5 ± 2	11±4*	4 ± 2	9 ± 4‡	0.89	0.05	0.05
TMP (mmHg)	3 ± 2	6 ± 3	3 ± 2	3 ± 4	4 ± 1	9 ± 4*	3 ± 2	3 ± 2	3 ± 3	12±3*	4 ± 3	5 ± 2*	0.87	<0.0001	0.02
PVR (wood units)	0.7 ± 0.3	0.6 ± 0.1	0.8 ± 0.3	0.4 ± 0.3	0.9 ± 0.3	0.7 ± 0.4	1.2 ± 0.5	0.8 ± 0.5*	1.3 ± 0.5*	0.9 ± 0.3*	1.3 ± 0.4	1.0 ± 0.3*	0.0008	0.006	0.0001
SVR (dynes/s•cm⁵)	1185±250	439±68	969±315‡	619±222	1490±287*	542±130	1203±326‡	851±285*	1562±304*	680±153*†	1283±347*‡	925±232*	0.0009	<0.0001	0.005
PAC (ml/mmHg)	12±1	12±4	11±4	14±4	9 ± 1	8 ± 3	8 ± 2*	10±3*	6 ± 1*†	5 ± 4*	7 ± 2*	7 ± 2*†	<0.0001	0.0002	<0.0001
SAC (ml/mmHg)	2 ± 0	2 ± 1	2 ± 0	3 ± 1	2 ± 0	2 ± 1	2 ± 0‡	2 ± 1	1 ± 0*	1 ± 0*	1 ± 0*	1 ± 0*†	0.02	0.03	<0.0001

Values are mean ± SD or n (%).

HR, heart rate; MAP, mean arterial pressure; A-V O₂ difference, Arterio-Venous oxygen difference; SV, stroke volume; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; DPG, diastolic pressure gradient; Cut-off values for PCWP were >25 mmHg for exercise and > 18 mmHg for saline infusion; NA, not applicable; CVP, central venous pressure; TMP, transmural filling pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; PAC, pulmonary arterial compliance; SAC, systemic arterial compliance.

For between groups comparison **P*<0.05 vs < 40 years; †*p*<0.05 vs 40–59 year; differences between baseline and re-baseline was tested with paired *t*-test ‡*p*<0.05.

For normally distributed data ANOVA was used to assess between group differences and Tukey HSD test was used to test which group means differed.

Pearson chi-square test was used in case of categorical data.

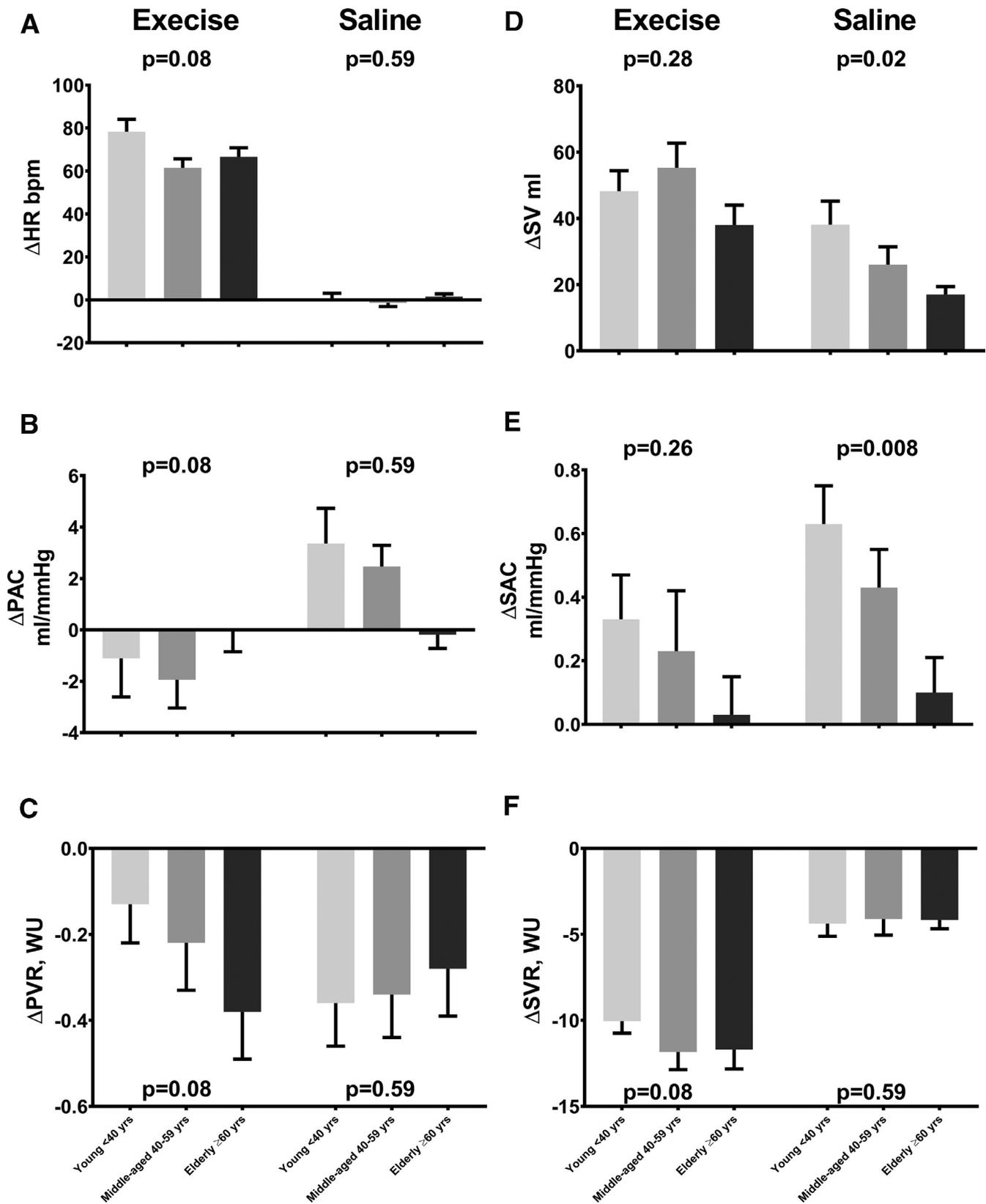


Fig. 1. Bar chart showing hemodynamic changes for each age groups (young, middle-aged and elderly) at exercise and rapid saline infusion for [A] heart rate (ΔHR), [B] pulmonary arterial compliance (ΔPAC), [C] pulmonary vascular resistance (ΔPVR) expressed as wood units (WU), [D] stroke volume (ΔSV), [E] systemic arterial compliance (ΔSAC) and [F] systemic vascular resistance (ΔSVR) expressed as WU. Error bars reflect SEM. Between-group differences were tested by ANOVA.

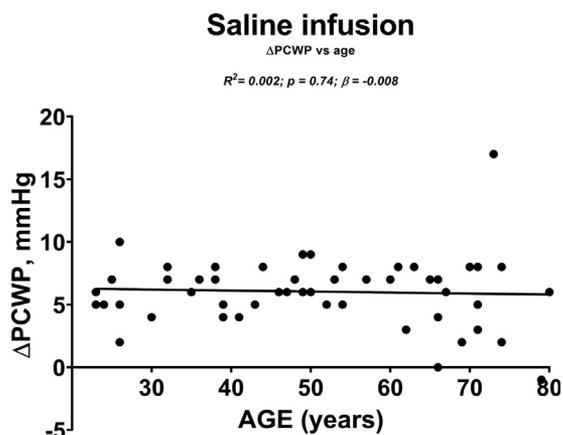


Fig. 2. Change in pulmonary capillary wedge pressure (Δ PCWP) after rapid saline infusion vs age ($R^2=0.002$; $p=0.74$; $\beta=-0.008$). The solid line represents a linear relationship between variables. Reported p -value reflect testing for association between Δ PCWP and age by linear regression.

pressures, [Table 2](#). PCWP increased in all three groups (Δ PCWP 6 ± 2 ; 7 ± 2 ; 6 ± 4 mmHg, young, middle-aged and elderly respectively, within group differences $p < 0.0001$ for all 3 groups, between group difference $p = 0.68$). There was no correlation between age and PCWP before or after rapid saline infusion ($r=0.06$; $p=0.68$ and $r=0.01$; $p=0.94$, respectively) similarly there was no association between Δ PCWP and age ($r=0.05$; $p=0.74$; [Fig. 2](#)). Nineteen participants (38%) increased their PCWP to more than 15 mmHg and 6 participants (12%) to more than 18 mmHg.

The increase in PCWP relative to the volume of infused saline was similar across all three age groups ($p=0.73$; [Fig. 3A](#)) which is opposed to low-level exercise where the groups were already differentiated ([Fig. 3B](#)). We found no gender differences in the hemodynamic response to rapid saline infusion at any age group. When comparing young males to elderly females we did not see any difference in the increase in PCWP relative to volume infused ($p=0.78$).

Similar to PCWP, CVP increased significantly with rapid saline infusion in all three groups (Δ CVP 7 ± 4 ; 7 ± 2 ; 5 ± 2 mmHg, young, middle-aged and elderly respectively, within group differences $p < 0.0001$ for all 3 groups). This increase in CVP was similar and in parallel with PCWP resulting in no difference in the gradient between PCWP and CVP after rapid saline infusion ([Fig. 4](#) panel a-c).

Despite correlation between age and PVR ($r=0.52$; $p < 0.0001$) and age and SVR ($r=0.44$; $p=0.03$), rapid saline infusion caused an age-independent decrease in SVR (-350 ± 223 ; -317 ± 271 ; -333 ± 164 dynes/s \cdot cm 5 ; young, middle-aged and elderly respectively; $p=0.93$) and age-independent decrease in PVR (-0.4 ± 0.4 ; -0.3 ± 0.3 ; -0.3 ± 0.5 WU; young, middle-aged and elderly respectively; $p=0.85$). On the contrary, rapid saline infusion caused an increase in PAC and SAC in the young but this improvement was ameliorated by increasing age ($r=-0.34$; $p=0.02$ and $r=-0.46$; $p=0.001$; PAC and SAC respectively). This age-dependent differences in compliances were driven by an age-dependent impairment in SV response ($r=-0.44$; $p=0.002$). At re-baseline, before rapid saline infusion we observed no differences in pulmonary pressures or

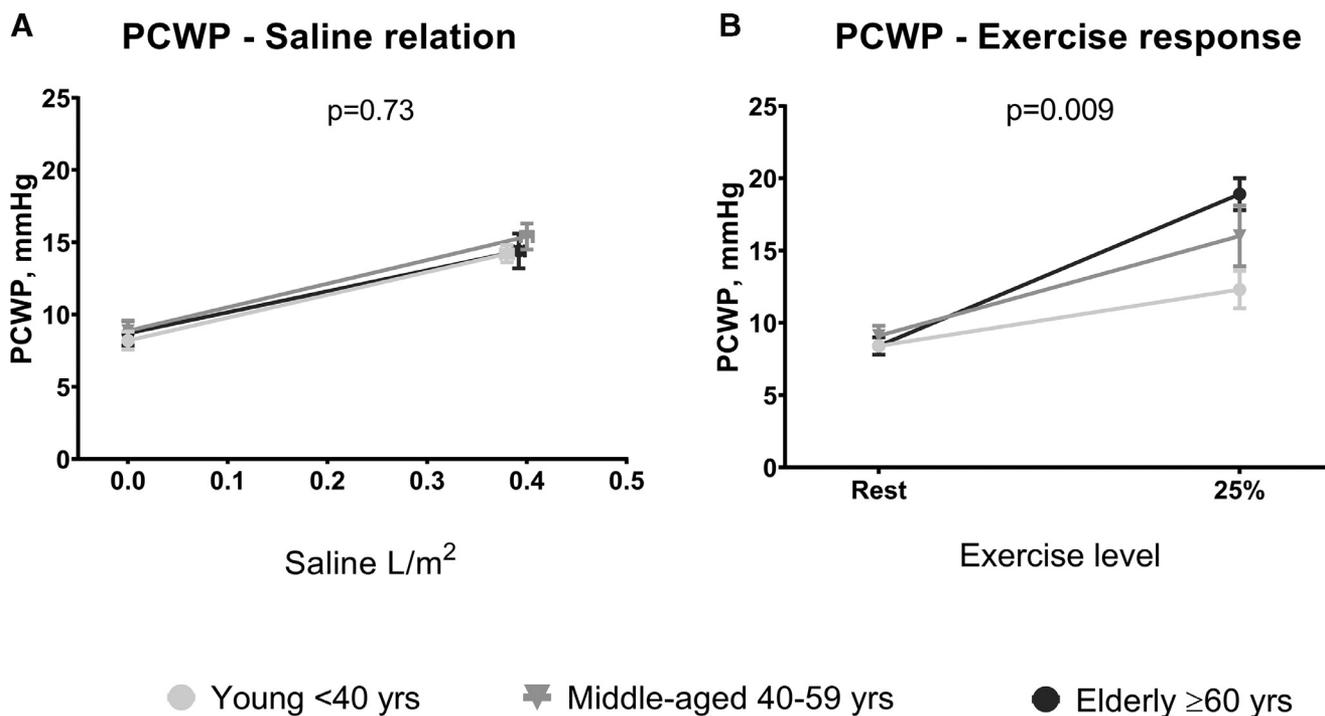


Fig. 3. Pulmonary capillary wedge pressure relative to [A] saline infused and [B] Exercise from baseline to 25% of peak VO_2 in young <40 years (round symbol), middle-aged 40–59 years (square symbol) and elderly 60–80 years (triangular symbol). Error bars reflect SEM. Between-group differences were tested by ANOVA.

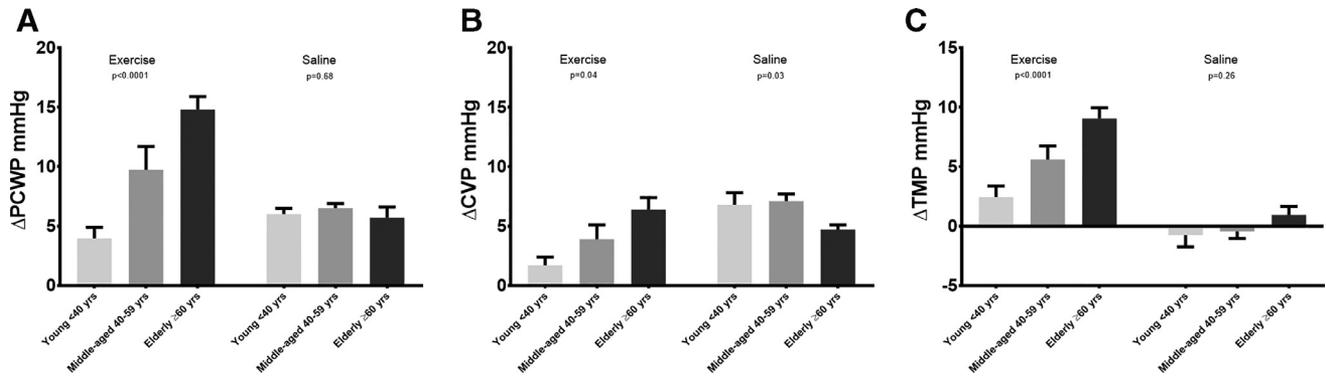


Fig. 4. Bar chart showing hemodynamic changes for each age group (young, middle-aged and elderly) at exercise and rapid saline infusion for [A] pulmonary capillary wedge pressure (Δ PCWP), [B] central venous pressure (Δ CVP) and [C] transmural filling pressure (Δ TMP). Error bars reflect SEM. Between-group differences were tested by ANOVA.

resistances compared to the original baseline values, but slightly higher HR, CO and decreased MAP and SVR. This was present in all three age groups but more pronounced in the elderly. We found no significant correlations between echocardiographic parameters (E/e' , TAPSE, E, A or filling pressures) and PCWP in any of the three age groups (all $p > 0.05$).

Safety

We observed no adverse events related to catheterization or wedging during exercise. No participant experienced dyspnea or other signs of pulmonary edema during or after rapid saline infusion.

Discussion

The major finding is that exercise causes an age-dependent increase in PCWP whereas rapid saline infusion causes an age-independent increase in PCWP, suggesting that age-related impairments beyond passive stiffness have a greater impact on exercise-induced increase in PCWP.

Hemodynamic Responses with Rapid Saline Infusion and Exercise

The absent age-related difference in PCWP after rapid saline infusion is interesting as age-related differences in PCWP and TMP were seen with exercise. As heart rate increases, the duration of systole is relatively constant whereas the duration of diastole is shortened to almost 1/3.¹⁴ Hence the heart has to move a larger volume of blood from the atria to the ventricles in shorter time during ventricular diastole testing the diastolic reserve.¹⁵⁻¹⁷ It is well known that there are age-related impairments in diastolic function.¹⁸⁻²⁰ Since rapid saline infusion predominantly tests passive diastolic ventricular compliance, other factors than impairments in passive ventricular compliance contribute to the observed age-related differences in filling pressures with exercise.

Age attenuates the lusitropic effect of exercise slowing the active relaxation of the ventricle by several

mechanisms. Age attenuates the autonomic nervous system, this slows the influx of Ca^{2+} into the sarcoplasmic reticulum hereby slowing the breakage of the actin-myosin cross-linkage.^{21,22} Age also attenuates the exercise-induced augmentation in LV torsion the so-called “spring-effect” slowing the rapid untwisting and elastic recoil of the LV further impairing LV filling.²³ Our data suggest that filling pressure is more affected by changes in active relaxation compared to changes in passive relaxation. It should be recognized, however, that filling pressure is not only affected by active relaxation. Age-related increases in arterial stiffness alter loading conditions of the ventricles, and we noted a larger increase in pulse pressures in the elderly, suggesting that ventriculo-vascular coupling might also be of importance.^{24,25}

Rapid saline infusion caused almost identical increases in PCWP and CVP. This parallel increase in left and right filling pressures meant that the gradient between PCWP and CVP remained unchanged. In the absence of any significant pericardial disease, this gradient is also known as the transmural filling pressure, TMP (true distending LV pressure).^{26,27} The inability of the pericardium to acutely accommodate the volume infused results in an increase in pericardial pressure, and as pericardial pressure affects all chambers of the heart, parallel increases in CVP and PCWP. These observations are in concordance with observations made by other researchers. D’Alto et al. performed right heart catheterization in patients referred for suspicion or evaluation of pulmonary hypertension before and after rapid saline infusion of 7 mL/kg over 5 to 10 min.²⁸ They found that rapid fluid loading only resulted in minor increases in TMP in the control groups whereas patients with postcapillary pulmonary hypertension had significant increases in TMP. Similar results were observed by Andersen et al. in patients with preserved ejection fraction referred due to unexplained dyspnea, they found significant larger increases in TMP in subjects with post capillary hypertension (heart failure with preserved ejection fraction).⁶

Contrary to the present study, Fujimoto et al.⁵ observed age and sex differences with regards to the PCWP-saline

relationship in healthy sedentary adults. The slope of PCWP-saline relationship in the present study was steeper (14–16 mmHg/L/m²) compared to the Fujimoto et al. (11–12 mmHg/L/m²). In the present study a smaller volume of saline was infused (10 ml/kg vs ≈13–14 ml/kg) at similar speeds and as demonstrated by Fujimoto, the PCWP-saline response does not seem to be linear, but with steeper slope initially with a gradual decline.⁵ We did not observe any gender-related differences with regards to PCWP or in the PCWP-saline relationship.

Stroke Volume and Pulmonary Circulation

Similar to previous reports, rapid saline infusion produced a greater hemodynamic effect on the pulmonary circulation compared to exercise.^{5,29} Irrespective of age, rapid saline infusion caused small increase in pulmonary pulse pressure with a relative greater increase in stroke volume resulting in a significant increase in PAC. Interestingly, this positive effect was driven primarily by the younger age group as the effect of rapid saline infusion on SV was attenuated in the elderly. Impaired SV response coupled with a larger increase in pulmonary PP in the elderly indicates decreased compliance in the pulmonary vasculature with increasing age. This is in accordance with previous histological and clinical studies describing age-related pulmonary vascular remodeling and age-related stiffness of the pulmonary vasculature.^{30–32} There is no age-related difference in the change of PVR between stressors indicating a more fixed resistance in the pulmonary circulation that is not ameliorated by physiologic vascular recruitment during exercise. With exercise, SV response was preserved with no difference across the age groups but at the cost of increased filling pressure with increasing age.

The hemodynamic response to rapid saline infusion presented here provide normative ranges across age groups. The results can help discern between physiological aging and an abnormal response due to cardiovascular impairment when performing rapid saline infusion in the catheterization laboratory. This is of importance in heart failure with preserved ejection fraction where knowledge of normal physiologic response to stress is important as hemodynamic stressors are used for diagnostic purposes. Due to the differences in hemodynamic response, a rapid fluid challenge might help clarify a borderline hemodynamic response to exercise. Even though exercise seems like a more sensitive stressor.⁶

Limitations

Our intent was to select healthy participants with average exercise habits to be as close to a “normal” background population as possible. Despite this, the included participants’ peak VO₂ was higher than sedentary age-matched controls. Furthermore, when selecting participants >60 years of age there might be a selection bias relative more fit and determined elderly participants. However, underlying undiagnosed cardiovascular or pulmonary

disease cannot be ruled out. The study did not evaluate the specificity or sensitivity of the two stressors to detect hemodynamic derangements suggestive of cardiovascular impairment or disease. The sample size is modest and therefore we cannot exclude the risk of a type II error. The present study assessed only one dose of rapid saline infusion and a different speed or volume of saline infusion may give a different hemodynamic response.

Despite waiting for the hemodynamic values to return to baseline after exercise and before re-baseline we observed reminiscent systemic vasodilation compared to the initial baseline hemodynamics. These changes were, however, minor and only seen in the systemic circulation, not in the pulmonary circulation. We consider that the main conclusions of the study are not affected. Participants were studied during semi-supine exercise, and results may differ with exercise performed in the upright position.

Conclusion

Unlike exercise, fluid loading causes an age-independent increase in left heart filling pressure in healthy adults.

Disclosures: All authors have nothing to disclose.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.cardfail.2019.06.004](https://doi.org/10.1016/j.cardfail.2019.06.004).

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