Impairments in Hemodynamic Responses to Orthostasis Associated with Frailty: Results from TILDA

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Abstract

Background: Dysregulated homeostatic response to stressors may underlie frailty in older adults. Orthostatic hypotension results from impairments in cardiovascular homeostasis and is implicated in falls and other adverse outcomes. This study aimed to characterise the relationships between orthostatic blood pressure (BP) and heart rate recovery and frailty in an older population.

Design: Cross-sectional study

Setting: Two health centres in the Republic of Ireland

Participants: 4334 adults aged 50 and older enrolled in The Irish Longitudinal Study on Ageing

Measurements: Continuous non-invasive BP responses during active standing were captured by Finometer®. Frailty was assessed using the Cardiovascular Health Study criteria. Linear mixed models (random intercept) with piecewise splines were used to model differences in the rate of BP and heart rate recovery.

Results: 93 (2.2%) participants were frail and 1366 (31.5%) were prefrail. Adjusting for age and sex, frailty was associated with a reduced rate of systolic BP recovery between 10-20 seconds post stand (frailty*time = -4.12 95%CI: -5.53 - -2.72) and with subsequent deficits in BP between 20-50 seconds. Similar results were seen for diastolic BP and heart rate. Further adjustment for health behaviours, morbidities, and medications reduced, but did not attenuate these associations. Of the 5 frailty criteria, only slow gait speed was consistently related to impaired BP and heart rate responses in the full models.

Conclusions: Frailty, and particularly slow gait speed, was associated with reduced rate of recovery in BP and heart rate recovery following active standing. Impaired BP recovery may represent a marker of physiological frailty.

Key words

Frailty, Orthostatic Hypotension, Aging, Blood pressure, Homeostasis

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Impact statement

We certify that this work is novel or confirmatory of recent novel clinical research. The potential impact of this research on clinical care or health policy includes the following: it highlights the relevance of impaired blood pressure regulation as a potential cause of adverse outcomes in older adults with signs of frailty, with implications for decision making around antihypertensive treatment. The results also show that slow gait speed captures physiological frailty at least was well as the overall phenotype criteria. More broadly, they tentatively suggest rate of recovery in blood pressure immediately post standing may be a useful way to assess physiological reserve in older adults.

Introduction

Levels of functional ability and risk of adverse health outcomes vary widely across older adults. This differential vulnerability among adults of the same age is often referred to as frailty.[1, 2] Frailty can be conceptualised as a syndrome of physiological dysregulation leading to a decreased ability to respond to homeostatic stressors, and recognisable as a phenotype comprising 5 related criteria: slow gait, muscle weakness, poor endurance or exhaustion, low physical activity and loss of (lean) body weight.[3]

Few studies have directly explored the relationships between this frailty phenotype and dynamic measures of homeostatic responses. Orthostasis, or standing up, is a mild physiological stressor requiring an integrative neuro-cardiovascular response to maintain blood pressure (BP) homeostasis in the face of large shifts in blood volume distribution.[4] Impaired responses can lead to excessive falls in BP known as orthostatic hypotension (OH). In analogy to frailty, OH may reflect various underlying health deficits and is predictive of adverse outcomes in older adults.[5, 6]

In previous studies OH, defined according to the consensus definition of a sustained drop of 20mmHg in systolic BP (SBP) or 10mmHg in diastolic BP (DBP) [7], was not related to physical frailty.[8, 9] However, frailty has been associated with lower heart rate variability, another sign of impaired autonomic control of the cardiovascular system, in older women.[10, 11]

Discrete BP measurements capture only a fraction of the full hemodynamic responses. Studies using continuous BP monitoring suggest aging is characterised by a gradual slowing of initial BP recovery post-standing, indicative of declining BP homeostatic function.[12] Recent data has linked impairments in early BP recovery to mortality in older falls clinic

patients.[13] Similarly, pilot data from a convenience sample of older Irish adults suggested possible relationships between orthostatic hemodynamics and frailty.[14]

We hypothesise the frailty phenotype and impaired orthostatic hemodynamics to be shared manifestations of an underlying physiological frailty. In addition, there may be direct mechanisms linking the physical frailty criteria to BP homeostasis, including loss of muscle mass and strength, impaired peripheral nerve function and/or declining central nervous co-ordination.[14]

This study aimed to characterise the BP and heart rate responses to orthostasis across levels of frailty within a large population sample of middle-aged to older adults and to assess the role of health conditions and medications in these relationships. We further aimed to explore the relationships between hemodynamic responses and the different frailty criteria.

Methods

Sample

The Irish Longitudinal Study on Ageing (TILDA) includes 8175 participants representative of the community living population aged ≥50 in Ireland. Households were selected in geographic clusters from a list of all residential addresses in Ireland. Each selected household was visited by an interviewer and any resident aged ≥50 as well as their spouse or partner were invited to participate. The household response rate was 62.0%. Each participant provided written informed consent. Those with severe cognitive impairment preventing meaningful consent were not included in the study. Approval for the study was obtained from the Trinity College Faculty of Health Sciences Research Ethics Committee.

Participants underwent a structured interview in their homes covering their health, lifestyle, social and financial circumstances. 5035 participants agreed to attend for a comprehensive health center assessment. The sampling procedure and health assessment have been described in detail previously.[15] Measures specific to the current analysis are detailed below.

Frailty

Frailty was assessed using an adaptation of the frailty phenotype.[3] The detailed methods used are reported elsewhere.[16] Briefly, the criteria were:

Slowness: The sex specific slowest 20% gait speed from participants aged ≥65 stratified by height, based on 16ft walk time. Cut-points were 109.7cm/s for men shorter than 173cm

and 116.7cm/s for men taller than 173cm. For women, they were 100.7cm/s for those shorter than 159cm and 108.4cm/s for those taller than 159cm.

Weakness: The sex specific lowest 20% grip strength from participants aged ≥65 stratified by body mass index (BMI). Cut-points were 20.5kg for men with BMI<24, 21.5kg for men with BMI of 24-26, and 23kg for men with BMI >26. For women, they were 11.5kg for those with BMI<23 and 13kg for those with BMI>23

Low Activity: The sex specific lowest 20% energy expenditure from participants aged ≥65, based on the International Physical Activity Questionnaire (IPAQ). Cut-points were <868 kcal/week for men and <309 kcal/week for women.

Exhaustion: Responding 'sometimes' or 'often' to the Centre for Epidemiological Studies Depression scale (CES-D) items "I could not get going" or "I felt that everything I did was an effort"

Weight loss: Self-reporting unintentionally losing ≥10lbs in weight in the last year.

Active stand protocol

Participants underwent a lying-to-standing orthostatic test (active stand) with non-invasive continuous beat-to-beat BP monitoring using digital photoplethysmography (Finometer® MIDI device, Finapres Medical Systems BV, Amsterdam, The Netherlands, www.finapres.com). After ten minutes' supine rest participants were asked to stand in a timely manner (<5 seconds) and were aided by a research nurse when necessary. After standing, SBP, DBP and heart rate were monitored for three minutes of quiet standing. The instrument calibration, data processing and feature extraction for this test have been described in detail previously.[12, 17, 18]

For analysis, beat-to-beat values were averaged according to the 5-second averages method to filter any noise.[19] Features were then extracted from each record. The algorithm captures BP and heart rate values at 10-second intervals up to 110 seconds post stand using the 5-second averages for each time-point. In addition, the lowest BP values (nadirs) and highest heart rate (maximum) are recorded. Baseline was defined as the mean value from 60-30 seconds prior to standing. From this data additional parameters were calculated, specifically the percentage of baseline recovered at each time-point and the maximum change (delta) in BP and heart rate during standing.

Other measures

Height and weight were measured using standard procedures and BMI defined as weight (kg) divided by height^2 (m). Participants reported doctor diagnoses of any cardiovascular conditions and gave a list of medications. Participants were also asked about health behaviors including smoking. Depressive symptoms were assessed using the 20-item CES-D,[20] the two items used in the frailty definition were excluded from analyses.

Statistical Analysis

Statistical analyses were performed in Stata version 14.2. Differences across frailty groups were assessed using Analysis of Variance (ANOVA) for normally distributed continuous variables, Kruskil-Wallis tests for non-normally distributed variables and Chi-squared tests for categorical variables.

Linear mixed effects models (Stata's 'mixed' command) with a participant level random intercept were used to model the recovery in BP or heart rate from 10-110 seconds post stand, comparable to modelling change over time in a longitudinal analysis.[21, 22] The primary outcome measure was the percentage of BP or heart rate recovered over the time standing. Residual variance across time was modelled using an autoregressive correlation matrix with a lag of 1 to account for stronger correlations between closer together time-points. Conceptually, the recovery of BP and heart rate can be broken down into an initial rapid recovery phase followed by a stabilisation and 'levelling off' towards the baseline. Consequently, we parameterised time using linear splines with knots at 20 and 30 seconds with the slopes between these knots representing the different phases of the stand (10s-20s, 20s-30s, 30s-110s).[21] These re-parameterized time variables were included in the models as fixed effects.

Main effects and interactions with the time variables were included for all predictors. The interaction term between frailty and time represents the effect of frailty on the *rate of recovery* with time in each period, that is to what extent frailty determines the slope of recovery over that time. To aid interpretation we additionally present conditional mean responses during the stand, ie the expected values of BP or heart rate recovery (% of baseline) across frailty groups over time holding all covariates constant at their means. The basic models included age (as linear and quadratic terms to account for the potential non-linear relationship) and sex. The full models additionally included fixed between-patient effects for BMI (linear and quadratic), smoking, antihypertensive (ATC codes C02 and C07) and antidepressant medications, depressive symptoms and self-reported cardiovascular conditions; hypertension, diabetes, stroke, heart attack, angina and heart murmur.

Relationships with the individual frailty criteria were modelled using the same approach. The full model outputs are provided in supplemental appendix tables SA1-7.

Results

Data on frailty and orthostatic BP responses were available for 4334 participants from the health center sample, with a mean (SD) age of 61.6 (8.2) years (Table 1). 2327 (53.7%) were female, 2674 (61.7%) had ≥1 cardiovascular conditions and 638 (14.7%) were current smokers (Table 1). 93 (2.2%) participants were frail and 1366 (31.51 %) prefrail. Frailer participants had higher BMI and depressive symptoms and levels of current smoking and medication use (all $p<0.001$).

The overall resting mean (SD) SBP was 136.2 (22.3) mmHg, DBP 73.3 (11.2) mmHg and heart rate 65.2 (10.1) beats per minute (bpm) (Table 1). There was a trend towards higher baseline SBP across the frailty groups, while baseline DBP was lower (Table 1). Baseline heart rate was higher in frail participants; 67.6 (10.3), compared to 64.7 (9.7) in robust ($p<0.001$). The maximum drop in SBP and DBP was similar across groups, while the maximum increase in heart rate was smaller in frail participants, 18.8 (8.2) compared to 20.1 (8.7) ($p=0.011$) in robust.

Table 1 shows the coefficients for the relationships between frailty category and rate of recovery for each phase of the stand for % baseline BP or heart rate recovered. Conditional values from the models are shown in Figure 1. After controlling for age and sex, frailty was associated a slower recovery rate between 10-20 seconds after standing in both SBP (-4.12%/10s 95%CI=-5.53, -2.72 in frail compared to robust; -0.99 (-1.37,-0.60) for prefrail) and DBP (frail: -5.26 (-6.87,-3.65); prefrail: -1.80 (-2.24,-1.36)). Correspondingly, frailty was associated with deficits of approximately 3-4% in SBP and DBP over the following 40 seconds (20-60 seconds post standing, Figure 1 & Table S1). DBP was actually higher relative to baseline at 10 seconds suggestive of a more gradual pattern of drop and recovery (Fig 1).

There was little difference in the rate of recovery between 20-30 seconds, but frailty was associated with a steeper slope from 30-110 seconds for SBP recovery, as BP continued to recover over this time in frailer people. The general patterns of results were similar using the BP values in mmHG at each time point, rather than the percentage of baseline as the outcome variables (Supplemental Table 2 and Figure 1). The models also suggested residual variance was higher in frailer people, especially for SBP (Appendix tables 1 & 2).

Further adjustment for BMI, smoking, depressive symptoms, cardiovascular conditions and medications partially reduced the differences in the initial recovery slopes in SBP and DBP (Table 2). Although much of the relationship remained, the associated deficits in SBP and DBP were reduced to 1-2% lower in frail compared to robust (Figure 1).

Heart rate was higher throughout standing in the frail and prefrail groups compared to robust reflecting the higher baseline (Supplemental Fig 1). In the main analysis, heart rate effectively mirrored the BP responses with a slower rate of decrease in heart rate (between 10-20 seconds) (Table 2). Heart rate was then slightly higher relative to baseline at 20 seconds with the difference between groups diminishing over the rest of the stand. As with BP further adjustment partially attenuated the slope from 10 seconds, although differences between groups at 20 seconds remained similar as adjustment also reduced the trend towards relatively lower peak heart rate at 10 seconds.

After adjustment for all covariates and the other frailty criteria, slow gait speed was associated with slower rate of recovery in BP and heart rate between 10-20 seconds (Table 3), and with deficits in SBP and to a lesser extent DBP throughout the following 40 seconds post standing (Figure 2). Slow gait was also associated with lower heart rate at 10s and higher values at 20 seconds post stand. Weight loss was associated with mild deficits in DBP

recovery. Exhaustion was associated with reduced recovery rate for SBP and heart rate, but not clearly with deficits at any time point (Table 3).

Discussion

Frailty was associated with slower BP and heart rate recovery following standing in this sample of community dwelling middle-aged to older adults. In general less than half the effect was explained by adjustment for health behaviours, morbidities and medication use. When considered separately only slow gait speed was consistently related to impaired SBP and to a lesser extent DBP and heart rate responses independently of cardiovascular morbidities, medication use and the other frailty criteria.

Frailty has been associated with (sub)clinical cardiovascular disease and with impaired autonomic cardiovascular control.[11, 23] However, previous analyses from TILDA and the Canadian Study of Health and Aging have not shown clear relationships between OH and physical frailty.[8, 9] The conventional OH measurement used in these studies is based on discrete measurements which do not detect the early transient BP responses. An earlier beat-to-beat monitoring study found univariate trends towards impaired SBP recovery in frailer participants in a convenience sample of older adults.[14] The present study extends these findings using more sophisticated statistical methods to better characterise BP behaviour within a larger sample drawn from a population representative survey.

An increasingly detailed theoretical framework links frailty or resilience to an individual's capacity to resist stressors.[1, 24, 25, 26] However, direct support is lacking, with the best evidence so far coming from impaired response to Oral Glucose Tolerance test in frail older women.[27] The reduced BP recovery rate associated with frailty in this study provides some further support for this hypothesis.

The general pattern in frailer participants was a blunted early response in both BP and heart rate consistent with poorer autonomic compensation mechanisms following the stress of standing, and associated with deficits of 3-4% in BP over 30-40 seconds during the 1st minute post stand. It is worth noting the relatively modest size of these differences across groups and their functional significance is not yet clear. The small mean deficits may also reflect the relatively large variance across frail participants.

Recent findings of excess mortality in older falls patients experiencing impaired early BP recovery post standing, suggest transient deficits or later stabilisation of BP may be a marker of underlying physiological impairment.[13] Similarly, elevated resting heart rate is associated with increased mortality rates and may reflect low physical fitness and subclinical cardiovascular disease.[28, 29] Previous data from TILDA outlined an association between slower orthostatic heart rate recovery and increased 4-year mortality risk.[22] These hemodynamic differences could also contribute directly to adverse outcomes like falls in frail older adults. Analyses from TILDA found increased 2-year falls risk associated with delayed or incomplete BP recovery.[30] In another study, greater drops in BP and higher resting heart rate were associated with increased risk of low energy fractures (suggestive of injurious falls) over 25 years.[31]

Adjustment for morbidities, health behaviours and medications only partially attenuated the differences in BP recovery rates, although deficits between frail and robust groups were reduced to 1-2%. The interpretation of this is unclear, it may be that impaired BP responses reflect both an intrinsic physiological frailty and the burden of associated health deficits.[32]

Of the 5 frailty criteria, only slow gait speed was consistently related to poorer BP and heart rate recovery in fully adjusted models. Slower gait is strongly related to subsequent health

outcomes in older adults and has been suggested as a measure of frailty in its own right.[33, 34] The lack of consistent association with the other criteria indirectly suggests slow gait may actually be a more useful measure of physiological frailty than the frailty phenotype composite.

There may also be specific mechanisms linking slower gait speed and impaired orthostatic BP responses. OH has been associated with poorer peripheral motor nerve function in older adults.[35] It has also been associated with increased burden of White Matter Hyperintensities (WMH) on Magnetic Resonance Imaging scans, thought to reflect cerebral small vessel disease, in late life depression.[36] A number of cross-sectional and longitudinal studies have linked these brain changes to mobility decline.[37-40]

The immediate clinical implications of these findings are that poorer orthostatic BP regulation should be considered as a possible cause of falls in frailer older adults before instigating more intensive BP control as in the SPRINT trial.[41] More broadly they suggest a single mobility test provides sufficient information on physiological frailty to aid clinical decision making. Work from TILDA increasingly indicates the rate of recovery in BP and heart rate to be more informative than the size of initial drops in older adults.[22, 30] And, if validated further, non-invasive measures of BP homeostasis could provide a quick and effective means to assess physiological reserve.

Strengths of this study include the high quality assessments of frailty and orthostatic responses within this large sample and the breadth of data collected on potential confounding variables. The mixed modelling approach used provides a useful summary of the BP responses, but further work is needed to more completely model variation in the

shape of responses, identify the most meaningful parameters and optimally account for varying correlations between time-points.

The study also has some general limitations. It was not possible to control for factors that influence BP such as feeding or hydration status, although these factors did not affect BP behavior in a sub-study.[42] The mean age of the sample was 61.6 years and participants attending the health assessment were generally healthier than those who declined, limiting the prevalence of frailty. Despite the large overall sample the relatively small number of frail participants may have limited statistical power as well as the generalizability of the findings within the relatively young Irish population. The comparative healthiness of the sample may partially explain the modest size of effects. The cross-sectional design precludes determination of the causal direction of relationships. Findings were based on almost exclusively Caucasian Irish adults and should be extrapolated beyond this setting with care.

In summary, physical frailty, and especially slow gait speed, is associated with impairments in early orthostatic BP and heart rate recovery in older adults. Future studies to further establish the utility of orthostatic hemodynamics as measures of physiological frailty and their relationship to mobility decline are warranted.

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- Irish Social Science Data Archive (ISSDA) at University College Dublin www.ucd.ie/issda/data/tilda/
- Interuniversity Consortium for Political and Social Research (ICPSR) at the University of Michigan http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/34315

Author Contributions

MOC performed the analysis and drafted the manuscript. GS, CF, contributed to data analysis. CF, CWF, RAK contributed to data acquisition. MOC, GS, CF, RRO, CWF, RAK conceived the study, contributed to interpretation of data and critical revision of article for important intellectual content and gave final approval for submission.

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Elements of Financial/Personal Conflicts	*Author 1 MO'C		Author 2 GS		Author 3 CF		Author 4 RRO	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation								
		X		X		X		X
Grants/Funds								
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Board Member								
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Patents								
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Personal Relationship								

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Elements of Financial/Personal Conflicts	*Author 1 CWF		Author 2 RAK		Author 3		Author 4	
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Employment or Affiliation								
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Patents								
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Personal Relationship								
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Supplemental data titles

Table S1: Conditional differences in blood pressure or heart rate recovery compared to robust category (% baseline)

Table S2: Model parameters for blood pressure and heart rate recovery following active standing (mmHg or heart rate)

Table S3: Conditional differences in blood pressure or heart rate recovery compared to robust category in (mmHg or heart rate)

Figure S1: Conditional mean blood pressure and heart rate responses across frailty categories (mmHg or heart rate)

Table SA1: Mixed effects models for SBP recovery (% baseline)

Table SA2: Mixed effects models for DBP recovery (% baseline)

Table SA3: Mixed effects models for heart rate recovery (% baseline)

Table SA4: Mixed effects models for SBP recovery (mmHg)

Table SA5: Mixed effects models for DBP recovery (mmHg)

Table SA6: Mixed effects models for heart rate recovery (heart rate)

Table SA7: Mixed effects models for BP & heart rate recovery by frailty criteria (% baseline)

Graphics

Table 1: Participant characteristics

	Overall n=4334	Robust n=2875	Prefrail n=1366	Frail n=93	P
Age (mean (SD))	61.6 (8.2)	60.5 (7.6)	63.4 (8.9)	68.0 (11.2)	<0.001[a]
Female (count (%))	2327 (53.7)	1537 (53.5)	738 (54.0)	52 (55.9)	0.86[b]
BMI (mean (SD))	28.5 (4.9)	28.2 (4.7)	29.1 (5.0)	29.3 (7.0)	<0.001[a]
Depressive symptoms (median (IQR))	3 (1 - 7)	3 (0 - 5)	5 (1 - 10)	10 (5 - 20)	<0.001[c]
Current smoker (count (%))	638 (14.7)	379 (13.2)	234 (17.1)	25 (26.9)	<0.001[a]
Any CVD condition (count (%))	2674 (61.7)	1678 (58.4)	924 (67.6)	72 (77.4)	<0.001[a]
On antihypertensives (count (%))	568 (13.2)	316 (11.0)	236 (17.4)	16 (17.8)	<0.001[a]
On antidepressants (count (%))	256 (5.9)	108 (3.8)	125 (9.2)	23 (25.6)	<0.001[a]
Baseline systolic BP (mean (SD))	136.2 (22.3)	135.8 (21.7)	136.9 (23.2)	138.6 (25.5)	0.15[a]
Max Δ systolic BP (mean (SD))	-39.3 (17.9)	-39.0 (17.4)	-39.8 (18.7)	-41.6 (19.3)	0.17[a]
Baseline diastolic BP (mean (SD))	73.3 (11.2)	73.6 (11.0)	72.7 (11.6)	71.4 (11.2)	0.016[a]
Max Δ diastolic BP (mean (SD))	-25.8 (10.3)	-25.9 (10.1)	-25.8 (10.8)	-25.0 (10.8)	0.74[a]
Baseline heart rate (mean (SD))	65.2 (10.1)	64.7 (9.7)	66.1 (10.7)	67.6 (10.3)	<0.001[a]
Max Δ heart rate (mean (SD))	19.8 (8.9)	20.1 (8.7)	19.3 (9.2)	18.8 (8.2)	0.011[a]

[a]ANOVA [b]Chi-square [c]Kruskil-Wallis

Table 2: Model parameters for blood pressure and heart rate recovery following active standing (% recovery)

		Frailty*Time (rate of recovery)		
	Intercept (10s difference)	10-20s	20-30s	30-110s
Systolic BP				
Model 1				
Prefrail	0.39 [-0.41,1.20]	-0.99 [-1.37,-0.60]***	0.01 [-0.38,0.39]	0.15 [0.06,0.25]**
Frail	0.29 [-2.58,3.17]	-4.12 [-5.53,-2.72]***	-0.25 [-1.65,1.15]	0.46 [0.10,0.82]*
Model 2				
Prefrail	0.44 [-0.40,1.28]	-0.88 [-1.29,-0.47]***	0.07 [-0.34,0.48]	0.10 [-0.00,0.20]
Frail	1.07 [-1.97,4.10]	-2.71 [-4.21,-1.21]***	-0.29 [-1.79,1.21]	0.27 [-0.12,0.66]
Diastolic BP				
Model 1				
Prefrail	0.80 [-0.01,1.61]	-1.80 [-2.24,-1.36]***	-0.18 [-0.62,0.26]	0.15 [0.05,0.24]**
Frail	2.77 [0.10,5.44]*	-5.26 [-6.87,-3.65]***	-1.17 [-2.77,0.42]	0.25 [-0.07,0.58]
Model 2				
Prefrail	0.55 [-0.31,1.40]	-1.39 [-1.86,-0.92]***	0.07 [-0.40,0.53]	0.10 [-0.00,0.20]
Frail	2.59 [-0.27,5.45]	-3.44 [-5.16,-1.71]***	-0.76 [-2.47,0.95]	0.09 [-0.26,0.44]
Heart rate				
Model 1				
Prefrail	-1.26 [-1.93,-0.59]***	1.74 [1.36,2.13]***	-0.03 [-0.41,0.35]	-0.06 [-0.14,0.01]
Frail	-2.02 [-4.20,0.16]	4.92 [3.73,6.11]***	-1.10 [-2.29,0.08]	-0.24 [-0.49,0.01]
Model 2				
Prefrail	-0.51 [-1.22,0.19]	1.22 [0.81,1.62]***	0.07 [-0.33,0.47]	-0.03 [-0.11,0.05]
Frail	0.70 [-1.64,3.03]	2.41 [1.12,3.70]***	-1.12 [-2.40,0.16]	-0.17 [-0.45,0.10]

Parameters are estimated from mixed effects models with linear splines. Interaction coefficients represent the difference in slopes or rate of recovery in blood pressure or heart rate at each stage of the active stand. Model 1: Age and sex, Model 2: Age, sex, BMI, smoking, depressive symptoms, self-reported CVD conditions, medication use *P<0.05, **P<0.01, ***P<0.001

Table 3: Model parameters for the relationships between frailty criteria and blood pressure and heart rate recovery (% baseline)

		Frailty*Time (rate of recovery)		
	Intercept (10s difference)	10-20s	20-30s	30-110s
Systolic BP				
Slowness	-0.72 [-2.12,0.68]	-2.33 [-3.02,-1.64]***	0.96 [0.27,1.65]**	0.22 [0.06,0.39]**
Activity	0.69 [-0.36,1.73]	-0.48 [-0.99,0.04]	-0.45 [-0.96,0.06]	0.06 [-0.06,0.18]
Grip	0.09 [-1.23,1.40]	-0.41 [-1.05,0.24]	0.56 [-0.09,1.20]	0.05 [-0.11,0.20]
Exhaustion	1.12 [-0.38,2.63]	-0.76 [-1.50,-0.02]*	-0.89 [-1.63,-0.16]*	0.11 [-0.07,0.29]
Weight loss	0.24 [-1.29,1.77]	-0.61 [-1.37,0.14]	-0.74 [-1.49,0.01]	0.03 [-0.15,0.21]
Diastolic BP				
Slowness	1.89 [0.45,3.32]**	-3.82 [-4.59,-3.04]***	0.70 [-0.07,1.47]	0.11 [-0.05,0.27]
Activity	0.64 [-0.43,1.71]	-0.56 [-1.14,0.02]	-0.64 [-1.21,-0.06]*	0.05 [-0.07,0.17]
Grip	-0.22 [-1.57,1.12]	-0.26 [-0.98,0.47]	0.66 [-0.07,1.38]	0.01 [-0.15,0.16]
Exhaustion	0.73 [-0.81,2.27]	-0.62 [-1.45,0.22]	-0.70 [-1.53,0.13]	0.12 [-0.05,0.30]
Weight loss	0.30 [-1.27,1.87]	-1.11 [-1.96,-0.26]*	-0.92 [-1.76,-0.07]*	0.05 [-0.13,0.23]
Heart rate				
Slowness	-1.76 [-2.96,-0.55]**	3.26 [2.57,3.96]***	-0.25 [-0.94,0.43]	-0.10 [-0.23,0.04]
Activity	0.26 [-0.63,1.16]	0.21 [-0.30,0.73]	0.04 [-0.47,0.55]	0.02 [-0.08,0.12]
Grip	0.29 [-0.84,1.41]	0.53 [-0.12,1.18]	-0.39 [-1.03,0.26]	-0.02 [-0.15,0.11]
Exhaustion	-0.64 [-1.93,0.65]	1.20 [0.46,1.95]**	0.47 [-0.26,1.21]	-0.09 [-0.24,0.06]
Weight loss	0.16 [-1.15,1.47]	0.05 [-0.71,0.80]	0.15 [-0.60,0.90]	-0.01 [-0.16,0.14]

Parameters are estimated from mixed effects models with linear splines. Interaction coefficients represent the difference in slopes or rate of recovery in blood pressure or heart rate at each stage of the active stand. Models include age, sex, BMI, smoking, depressive symptoms, self-reported CVD conditions, medication use. *P<0.05, **P<0.01, ***P<0.001

Figure legends:

Figure 1: Conditional mean blood pressure and heart rate responses across frailty categories (% baseline)

Data are conditional means and 95% confidence intervals estimated from mixed effects models. Model 1: Age and sex; Model 2: age, sex, BMI, smoking, antihypertensive and antidepressant medication use, depressive symptoms and CVD conditions.

Figure 2: Conditional differences in blood pressure and heart rate recovery according to the presence of each frailty criterion (% baseline)

Data are conditional differences and 95% confidence intervals relative to the reference not having the criterion estimated from mixed models. All models include age, sex, BMI, smoking, antihypertensive and antidepressant medication use, depressive symptoms and CVD conditions, and are mutually adjusted for the presence of the other frailty criteria.