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CLINICAL INVESTIGATION

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Myocardial oxygen supply and demand imbalance predicts mortality in older nursing home residents: The PARTAGE study

Paolo Salvi MD, PhD[1] | **Andrea Grillo MD, PhD**[2] | **Sylvie Gautier MD**[3] | **Carlos Labat BSc**[3] | **Lucia Salvi MD**[4] | **Filippo Valbusa MD**[5] | **Corrado Baldi MD**[6] | **Matteo Rovina MD**[6] | **Giulia Simon MD**[6] | **Lan Gao MD, PhD**[7] | **Isabella Tan PhD**[8,9] | **Bruno Fabris MD**[2,6] | **Renzo Carretta MD, PhD**[2,6] | **Alberto P. Avolio PhD**[8] | **Gianfranco Parati MD**[1,10] | **Athanase Benetos MD, PhD**[3,11]

[1]Department of Cardiology, Istituto Auxologico Italiano, IRCCS, Milan, Italy

[2]Department of Medical, Surgical and Health Sciences, University of Trieste, Italy

[3]CHRU-Nancy, Pôle "Maladies du Vieillissement, Gérontologie et Soins Palliatifs", Université de Lorraine, Nancy, France

[4]Medicina II Cardiovascolare, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

[5]Department of Internal Medicine, IRCCS Sacro Cuore - Don Calabria Hospital, Negrar, Italy

[6]Medicina Clinica, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy

[7]Department of Cardiology, Peking University First Hospital, Beijing, China

[8]Macquarie Medical School, Faculty of Medicine, Health and Human Science, Macquarie University, Sydney, Australia

[9]The George Institute for Global Health, Sydney, Australia

[10]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

[11]INSERM, DCAC u1116, Université de Lorraine, Nancy, France

Correspondence
Athanase Benetos, Department of Geriatrics, University Hospital of Nancy, 54511 Vandoeuvre-lès-Nancy, France.
Email: a.benetos@chru-nancy.fr

Gianfranco Parati, Department of Cardiology, IRCCS Istituto Auxologico Italiano, San Luca Hospital, Piazzale Brescia 20, 20149 Milan, Italy.
Email: gianfranco.parati@unimib.it

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Abstract

Background: A mismatch between myocardial oxygen supply and demand is the most common cause of ischemic myocardial injury in older persons. The subendocardial viability ratio (SEVR) can usefully estimate the degree of myocardial perfusion relative to left-ventricular workload. The aim of the present study was to evaluate the ability of SEVR to predict long-term mortality in the older population. Additionally, we aimed to identify the SEVR cutoff value best predicting total mortality.

Methods: This is a multicenter, longitudinal study involving a large population of individuals older than 80 years living in nursing homes. Patients with cancer, severe dementia, and very low level of autonomy were excluded from

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the study. Participants were monitored for 10 years. Adverse outcomes were recorded every 3 months from inclusion to the end of the study. SEVR reflects the balance between subendocardial oxygen supply and demand, and was estimated non-invasively by analyzing the carotid pressure waveform recorded by applanation arterial tonometry.

Results: A total of 828 people were enrolled (mean age: 87.7 ± 4.7 years, 78% female). 735 patients died within 10 years and 24 were lost to follow-up. SEVR was inversely associated with mortality at univariate Cox-regression model (risk ratio, 0.683 per unit increase in SEVR; 95% confidence interval (CI) [0.502–0.930], $p = 0.015$) and in a model including age, sex, body mass index, Activity of Daily Living index and Mini-Mental State Examination score (risk ratio, 0.647; 95% CI [0.472–0.930]). The lowest tertile of SEVR was associated with higher 10-years total mortality than the middle ($p < 0.001$) and the highest ($p < 0.004$) tertile. A SEVR cutoff value of 83% was identified as the best predictor of total mortality.

Conclusions: SEVR may be considered as a marker of "cardiovascular frailty." An accurate non-invasive estimation of SEVR could be a useful and independent parameter to assess survival probability in very old adults.

Trial Registration: NCT00901355, registered on ClinicalTrials.gov website.

KEYWORDS

aged 80 and over, aging, myocardial ischemia, nursing home, subendocardial viability ratio

INTRODUCTION

Ischemic heart disease is currently the leading cause of death in the older population.[1] Myocardial ischemia results from an imbalance between oxygen supply and demand. The ischemic myocardial damage related to atherosclerotic plaque rupture, ulceration, or erosion with resulting intraluminal thrombus in coronary arteries is certainly the best-known and most-studied type of cardiac ischemic event. However, ischemic myocardial damage or acute myocardial infarction can be also caused by a functional imbalance between myocardial oxygen supply and demand. The latter type of myocardial ischemic damage may occur due to numerous and very different etiopathogenetic mechanisms, among which a severe reduction in arterial oxygen content (due to anemia or hypoxemia), or an insufficient blood flow to the myocardium in relation to the myocardial oxygen needs. The above conditions can also lead to myocardial ischemic cell injury without the presence of atherosclerotic plaques, in the most severe cases resulting in the so-called type 2 myocardial infarction.[2] Myocardial ischemia and type 2 myocardial infarction, due to a mismatch between myocardial oxygen supply and demand, are the most frequent types of myocardial ischemic injury in persons 75 years and older[3] and are related to poor outcomes.[4]

Key points

- An imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis is the most frequent cause of ischemic myocardial injury in very old patients.
- Subendocardial viability ratio (SEVR) assessed by applanation tonometry is a useful and effective non-invasive index of the degree of myocardial perfusion adequacy with respect to left ventricular workload.

Why does this paper matter?

Higher SEVR values are associated with higher survival rates at 10-year follow-up, suggesting a possible role of myocardial oxygen supply–demand mismatch assessment in predicting overall mortality in older individuals.

This study provides convincing evidence that individuals over eighty with low SEVR values should be considered as "frail older people". Our results emphasize the need to identify appropriate targets for their management, and to provide individualized strategies of cardiovascular prevention and care.

The subendocardial viability ratio (SEVR, also known as the Buckberg index) is a useful and effective index of the degree of myocardial perfusion adequacy with respect to left ventricular workload. It was originally based on the analysis of the pressure curve recorded in the left ventricle and in the ascending aorta[5,6] during the course of cardiac catheterization. The advent of transcutaneous arterial tonometry makes SEVR assessment easier and more feasible in clinical practice, without the need for invasive measurements.

The aim of the present study was to evaluate the prognostic value of the imbalance between myocardial oxygen supply and demand, assessed through non-invasive SEVR, to predict increased longevity in very older persons living in nursing homes. Additionally, we aimed at identifying the SEVR cutoff value best predicting total mortality.

METHODS

Design

This study represents a branch of the PARTAGE (Predictive values of blood pressure (BP) and ARTerial stiffness in institutionalized very AGEd population) study. PARTAGE is a multicenter, longitudinal study aimed at determining the predictive value of BP and arterial mechanical parameters on total mortality as well as major cardiovascular events and cognitive decline in a large population of individuals aged 80 years and over living in nursing homes.[7,8] In the present study, we have considered the data coming from the research groups of Nancy (445 participants), Verona (152 participants), and Cesena (267 participants), due to the availability of more extensive follow-up (10 years).

The aim of the PARTAGE Study was to determine the predictive value of BP and non-invasive hemodynamic parameters for overall mortality and major cardiovascular events, in a population older than 80 years of age living in nursing home. Self-measurements of BP were required. In order to obtain a correct self-measurement of BP, patients characterized by severe dementia, as assessed through Mini-Mental State Examination[9] (MMSE) score <12 out of 30), and by low level of autonomy, as assessed through Activity of Daily Living[10] (ADL) score ≤2 out of 6 at the time of enrolment, were excluded from the study.

The protocol of this study was approved in Nancy, France by the "Comité de Protection des Personnes of Nancy" and in Italy by the "Comitato Etico Area Vasta Romagna" and "Comitato Etico della Provincia di Verona". All participants provided written informed consent. Participants were enrolled between January 2006 and June 2008 and were followed up for 10 years. Adverse outcomes were recorded every 3 months from inclusion to the end of the study.

Clinical data collection was performed during either face-to-face interviews or examination of patients' medical records. The follow-up was carried out by periodic visits to nursing homes, by telephone interviews with patients or relatives, by interviews with dedicated nursing staff, and evaluation of the databases of nursing homes and public health care system.

The primary endpoint was overall mortality during the follow-up period.

Arterial functional parameters

BP waveform was recorded at recruitment on right common carotid, brachial, radial, and femoral arteries using a validated, high-fidelity PulsePen® tonometer (DiaTecne srl, San Donato Milanese, Italy).[11,12] Tests began after a resting period of at least 15 min in supine position.

The pressure waveforms recorded at the carotid artery level by applanation tonometry were shown to be a reliable surrogate for invasive central aortic waveform.[11,13] Central aortic BP values were obtained by the integral of the carotid curve after calibration with brachial mean and diastolic BP measured non-invasively by a validated Omron 705IT sphygmomanometer (Omron Healthcare Co., Kyoto, Japan). The oscillometric BP measurements were assessed simultaneously with each tonometric pulse wave recording.

Mean arterial pressure was estimated from the integral of the brachial artery pressure waveform performed with the same PulsePen® tonometer.[14] Where brachial tonometry was not performed due to technical reasons or poor recording quality, a 40% form factor was used to estimate mean arterial pressure.[15]

Carotid-femoral pulse wave velocity was also assessed. Pulse wave velocity was automatically determined by dividing the carotid-to-femoral artery distance by the time difference between the respective delays in the onset of peripheral (femoral) and central (carotid) pulses in relation to the preceding R wave of an electrocardiographic recording.[11,12]

Subendocardial oxygen supply and demand ratio assessment (SEVR)

The SEVR represents an index relative to the balance between oxygen supply and demand in the subendocardium. As originally described by Buckberg and Hoffmann[5,6] with invasive catheterization, the area between the pressure curve in ascending aorta and the left ventricular pressure

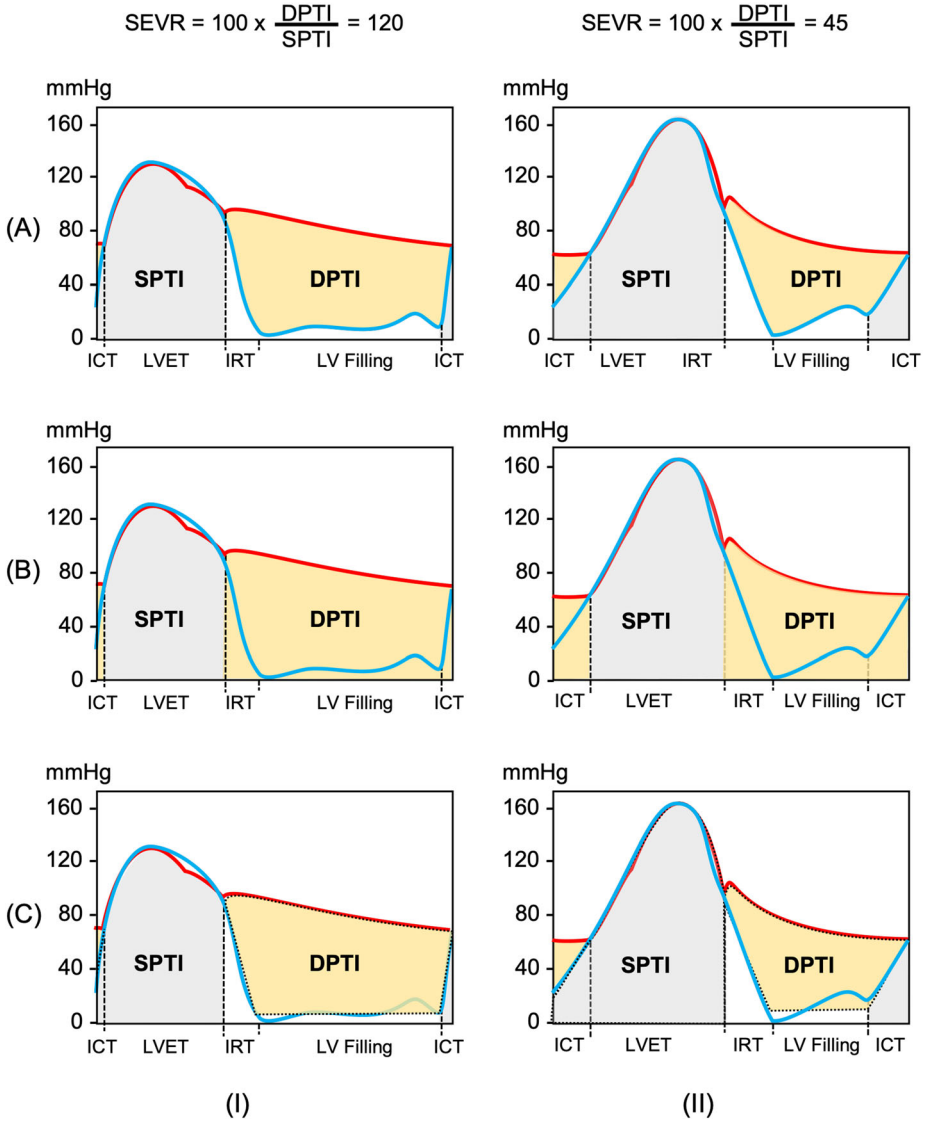

FIGURE 1 Subendocardial viability ratio (SEVR) assessed by invasive catheterization and estimated non-invasively by arterial tonometry. SEVR was calculated as diastolic pressure–time index (DPTI, yellow area) and systolic pressure–time index (SPTI, gray area) ratio. Blue lines show the left ventricular LV) pressure and red lines show arterial pressure in ascending aorta. Drawings on the left (I) show an example of SEVR in a patient with preserved viscoelastic properties of the large arteries. Drawings on the right (II) show the example of SEVR in a patient with arterial stiffness. Upper panels (A): SEVR assessed by invasive catheterization. DPTI represents the area between the aortic and LV pressure curves in diastole; SPTI represents the area under the systolic LV pressure curve, including LV isovolumic contraction time (ICT). Middle panels (B): non-invasive estimation of SEVR with arterial tonometry by the "traditional" method. DPTI and SPTI are estimated from the areas below the central pressure wave during diastole and during systole, respectively. Lower panels (C): SEVR estimated by the PulsePen® (DiaTecne srl, San Donato Milanese, Italy) tonometer (PulsePen® software, 2.3.2 version). DPTI is estimated from the area below the diastolic phase of the carotid pulse pressure curve, after subtracting the LV diastolic pressure area, ICT, and isovolumic relaxation times (IRT); SPTI is estimated from the area below the systolic phase of the carotid pulse pressure curve, to which the area related to the ICT is added. LVET, left ventricular ejection time.

curve during the diastolic phase (diastolic pressure–time index, DPTI) represents the oxygen supply to the subendocardium, while the area under the left ventricular pressure curve in systole (systolic pressure–time index, SPTI) represents the oxygen needs by the myocardium (Figure 1A). DPTI and SPTI therefore reflect subendocardial oxygen supply and demand, respectively, and their ratio (DPTI/SPTI) may represent a useful index of myocardial oxygenation (SEVR).

In our study, SEVR was estimated non-invasively by means of transcutaneous arterial tonometry using two different methods. (i) The "traditional" method (Figure 1B), usually implemented in arterial tonometers currently on the market, estimates the SEVR simply as the ratio of the

areas below the central aortic pressure wave during diastole (surrogate for DPTI) and during systole (surrogate for SPTI), respectively. (ii) A new method (Figure 1C), was recently developed and validated in an attempt to make the estimation of non-invasive SEVR more concordant with the invasively measured SEVR by catheterization.[16] In this improved method, DPTI was estimated from the area beneath the diastolic phase of the carotid pulse pressure curve, from which the areas corresponding to the areas under the ventricular pressure curve during isovolumic contraction and isovolumic relaxation phase and the area relating to the left ventricular diastolic pressure were subtracted. Isovolumic contraction time was estimated according to a validated formula based on carotid-femoral pulse wave velocity.[17] Isovolumic relaxation time and left ventricular mean diastolic pressure were automatically estimated by the PulsePen® software (2.3.2 version) (DiaTecne srl, San Donato Milanese, Italy) by a proprietary validated algorithm.[16] Similarly, SPTI was estimated from the area below the systolic phase of the carotid pulse pressure curve, to which the area related to isovolumic contraction time is added.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) for variables with normal distribution (evaluated with Kolmogorov–Smirnov test) and as median and interquartile range in cases of non-normally distributed data. Categorical data are shown as frequencies and proportions. Differences in anthropometric and clinical variables were tested between patients with first tertile and patients with second and third tertile of SEVR values. The unpaired t-test was used to compare normally distributed data while the homogeneity of variances was assessed by Levene's Test for Equality of Variances. The Mann–Whitney test was used to compare data with non-normal distribution and the χ^2 (Fisher's test in cases of an expected frequency <5) for categorical variables.

The occurrence of total mortality according to tertiles of SEVR was estimated using Kaplan–Meier curves for graphic representation and compared by the log-rank test. Cox regression multivariate models were used to assess the relative risk (hazard ratio and 95% confidence interval) of total mortality, according to each parameter considered as a continuous or discrete variable. Non-linearity in the relationship between continuous measures of the SEVR and risk of mortality was assessed using restricted cubic splines regression model. Data were fitted by a restricted cubic spline Cox proportional hazards regression model, and the model was conducted with 4 knots at the 5th, 35th, 65th, and 95th percentiles of SEVR (reference is the 5th percentile).

Univariate analysis was performed to determine factors associated with total mortality. Variables that were associated at the 0.20 significance level with total mortality were subsequently included in the multivariate Cox models. The proportional hazards assumption was assessed on the basis of a test of Schoenfeld residuals with the Cox regression. Sensitivity and specificity of SEVR to predict total mortality were analyzed by ROC (receiver operating characteristic) curve, and Youden's J statistic was used as criterion for selecting the optimum cut-off value. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS v.20 statistical software package (SPSS Inc., Chicago, IL).

RESULTS

Among the 864 patients included in the study, 36 individuals (5 males) were excluded from the study because they had not performed a complete recording at both carotid and femoral arterial sites (30), or because of poor quality of the signal (4), or the appearance of bigeminal rhythm (2). Statistical analysis was then performed on a total of 828 participants, 78% females, with a mean age (±SD) of 87.7 ± 4.7 years. 735 patients died within 10 years of study enrolment, 69 patients (60 females and 9 males) completed the 10-year follow-up and 24 were lost to follow-up. Table 1 shows the main clinical characteristics of participants. Differences between participants with respect to sex are shown in Supplemental Material, Table S1. No relationship was found between SEVR values and ADL and MMSE scores (see Supplemental Material, Figure S1 and S2, respectively). Atrial fibrillation arrhythmia was present in 104 participants in the study (= 12.6%) homogeneously distributed with respect to the tertiles of SEVR values. These patients were excluded in the first data analysis. In the second phase, patients with atrial fibrillation were also included. The results of the two analyses were totally overlapping, therefore the results presented below also include patients with atrial fibrillation.

Figure 2A shows the survival curves for total mortality according to the SEVR tertiles. The lowest tertile of SEVR (SEVR<83%) was associated with higher total mortality than the middle ($p < 0.001$) and the highest ($p < 0.004$) tertile. The results obtained in the 5 and 7-year follow-up were totally comparable to those obtained in the 10-year follow-up. The search for the SEVR threshold as a predictor of mortality showed a better sensitivity and specificity for SEVR values below 83%

TABLE 1 Clinical characteristics of the overall population and divided into tertiles of SEVR values.

Parameter	Pooled	T1	T2	*p*-value T2 versus T1	T3	*p*-value T3 versus T1
Participants; *N*	828	276	276		276	
Sex; females (%)	647 (78.1%)	233 (84.4%)	224 (81.2%)	0.310	190 (68.8%)	<0.0001
Weight; kg	62 (55–71)	61 (54–72)	63 (55–70)	0.594	63 (55–70)	0.574
Height; cm	157 (150–163)	156 (150–163)	156 (150–162)	0.955	158 (153–165)	0.002
BMI; kg/m^2	25.0 (22.3–28.5)	25.1 (22.1–28.9)	25.3 (22.9–28.8)	0.562	24.7 (22.1–27.9)	0.164
MMSE; score/30	24.8 (20.0–28.0)	24.0 (20.0–27.0)	25.0 (21.0–28.9)	0.030	25.0 (19.5–28.0)	0.505
ADL; score/6	5.5 (4.5–6.0)	5.5 (4.5–6.0)	5.5 (4.5–6.0)	0.274	5.5 (4.5–6.0)	0.208
Age; years	86.9 (84.2–91.3)	87.1 (84.7–91.7)	86.9 (84.0–91.0)	0.176	86.7 (84.0–91.2)	0.069
SBP; mmHg	136 (124–149)	140 (126–155)	137 (127–148)	0.100	132 (119–145)	<0.0001
DBP; mmHg	70 (63–78)	69 (61–77)	72 (63–78)	0.087	71 (65–80)	0.001
Heart Rate; bpm	68 (61–76)	77 (70–83)	68 (62–73)	<0.0001	61 (55–67)	<0.0001
Mean BP; mmHg	96.8 (88.4–107.2)	97.9 (89.4–108.7)	96.8 (90.2–107.0)	0.623	96.2 (87.0–105.8)	0.079
SPTI	38,959 (34297–44,356)	39,000 (33939–44,807)	39,479 (34704–44,563)	0.347	38,411 (33709–43,633)	0.001
DPTI	35,883 (29173–44,106)	27,635 (23638–31,759)	36,507 (31859–41,389)	0.062	46,163 (40028–53,222)	0.008
SEVR; %	92.2 (77.7–106.6)	72.6 (65.6–77.7)	92.2 (87.3–96.8)	<0.0001	117.1 (106.7–130.0)	<0.0001
cf-PWV; m/s	13.3 (10.5–16.7)	15.1 (12.2–18.1)	13.2 (10.4–17.1)	<0.0001	11.8 (9.6–14.5)	<0.0001
Clinical data						
Coronary AD	191 (23.1%)	61 (22.1%)	62 (22.8%)	0.838	67 (24.3%)	0.545
Heart Failure	144 (17.4)	51 (18.5%)	49 (17.8%)	0.825	44 (15.9%)	0.430
Cerebrovascular dis.	132 (15.9%)	45 (16.3%)	43 (15.6%)	0.126	44 (15.9%)	0.876
Peripheral AD	59 (7.1%)	23 (8.3%)	14 (5.1%)	0.816	22 (8.0%)	0.908
Atrial Fibrillation	104 (12.6%)	34 (12.3%)	31 (11.2%)	0.692	39 (14.1%)	0.530
Pacemaker	53 (6.4%)	26 (9.4%)	13 (4.7%)	0.031	14 (5.1%)	0.049
Diabetes	146 (17.6%)	58 (21.0%)	46 (16.7%)	0.191	42 (15.2%)	0.077
Hypertension	679 (82.0%)	237 (85.9%)	225 (81.5%)	0.167	217 (78.6%)	0.026
Dyslipidaemia	218 (26.4%)	67 (24.5%)	71 (25.7%)	0.731	80 (29.0%)	0.230
Current smoking	32 (3.9%)	9 (3.3%)	9 (3.3%)	1.000	14 (5.1%)	0.287
Previous smoking	145 (17.6%)	49 (17.8%)	40 (14.5%)	0.298	56 (20.4%)	0.448
Parkinson	29 (3.5%)	4 (1.4%)	11 (4.0%)	0.067	14 (5.1%)	0.017

(Continues)

TABLE 1 (Continued)

Parameter	Pooled	T1	T2	*p*-value T2 versus T1	T3	*p*-value T3 versus T1
Treatment						
α-blockers	43 (5.2%)	11 (4.0%)	15 (5.4%)	0.422	17 (6.2%)	0.245
β-blockers	150 (18.1%)	55 (19.9%)	54 (19.6%)	0.432	41 (14.9%)	0.279
CCB	206 (24.9%)	66 (23.9%)	78 (28.3%)	0.228	62 (22.5%)	0.404
ACE inhibitors	251 (30.3%)	83 (30.1%)	74 (26.8%)	0.396	94 (34.1%)	0.316
ARBs	163 (19.7%)	57 (20.7%)	61 (22.1%)	0.678	45 (16.3%)	0.188
Diuretics	483 (58.3%)	163 (59.1%)	170 (61.6%)	0.543	150 (54.3%)	0.264
NSAIDs	340 (41.1%)	116 (42.0%)	108 (39.1%)	0.793	116 (42.0%)	0.779
Anticoagulants	109 (13.2%)	42 (15.2%)	29 (10.5%)	0.098	38 (13.8%)	0.629
Insulin	40 (4.8%)	20 (7.2%)	10 (3.6%)	0.060	10 (3.6%)	0.060
Antidiabetic drugs	86 (10.4%)	37 (13.4%)	30 (10.9%)	0.590	19 (6.9%)	0.018
Statins	114 (13.8%)	37 (13.4%)	44 (15.9%)	0.400	33 (12.0%)	0.609

Abbreviations: AD, artery disease; ADL, Katz Index of Independence in Activities of Daily Living; ARBs, Angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CCB, calcium channel blockers; cf-PWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; DPTI, diastolic pressure–time index; MMSE, Mini Mental State Examination (Folstein' test); NSAIDs, Nonsteroidal anti-inflammatory drugs; SBP, systolic blood pressure; SEVR, subendocardial viability ratio; SPTI, systolic pressure–time index; T1 T2 T3, tertiles of the SEVR values.
Note: Data are expressed as median (interquartile range Q1–Q3) or number (%), where indicated.

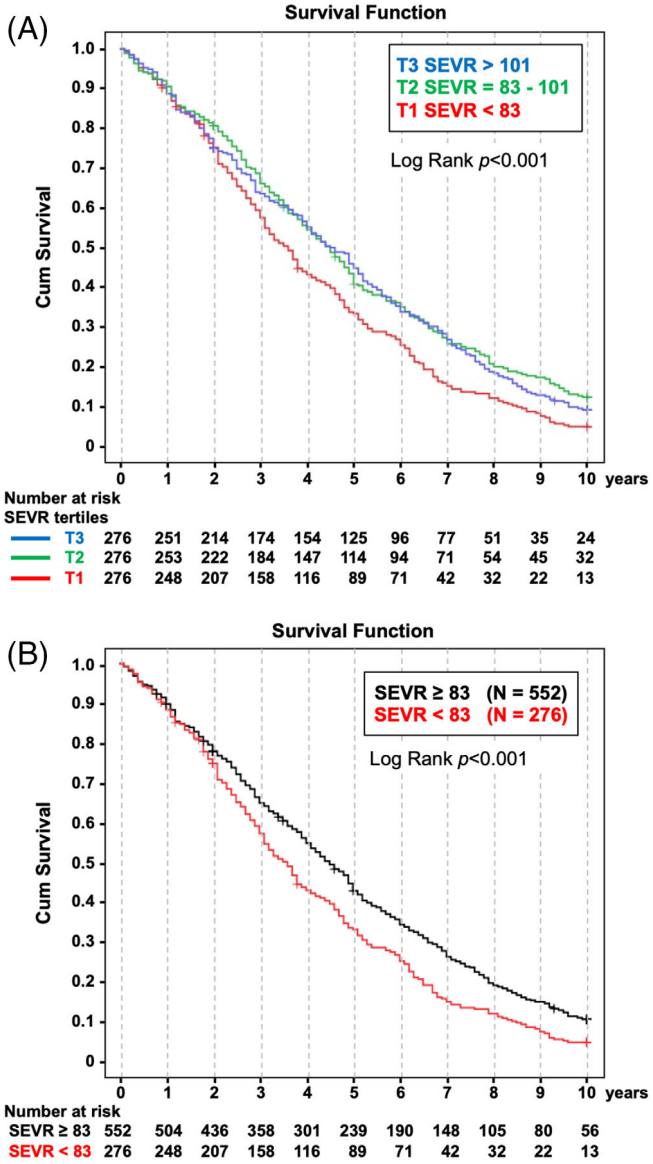

FIGURE 2 Survival curves (Log-rank analyses) for total mortality according to the tertiles of subendocardial viability ratio (SEVR). In the upper panel (A), the red line shows the 10-year follow-up survival of patients at the low tertile (T1) of SEVR; the green line shows the survival of patients at the medium tertile (T2) of SEVR; the blue line shows the survival of patients at the high tertile (T3) of SEVR. In the lower panel (B), the red line shows the 10-year follow-up survival of patients at the low tertile (T1), while the black line shows the survival of patients with SEVR values>83% (i.e., T2 + T3).

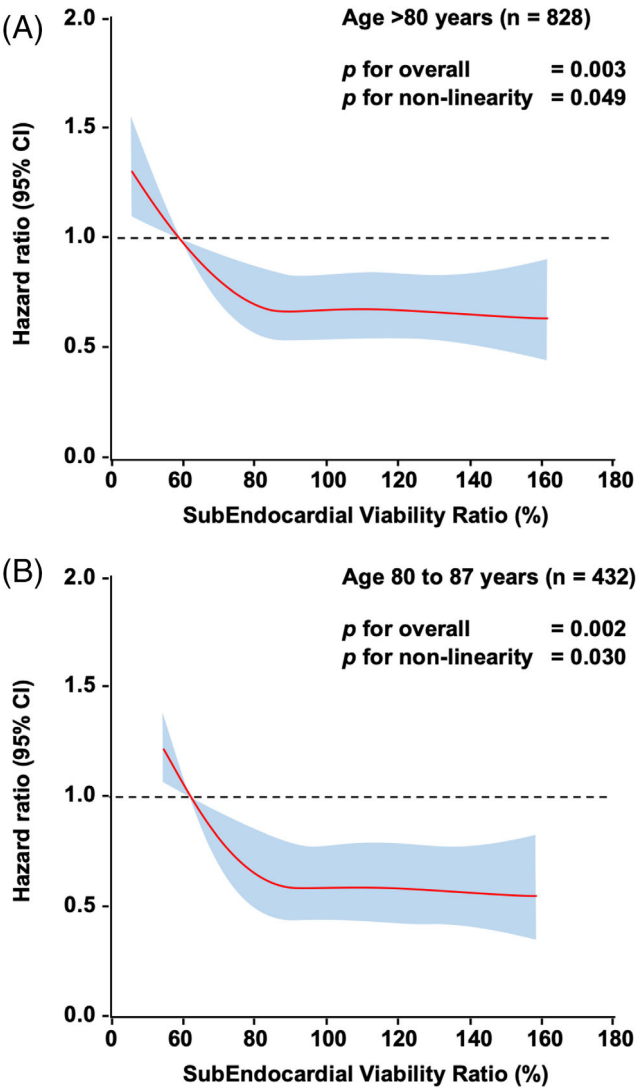

FIGURE 3 Association between continuous measures of the subendocardial viability ratio (SEVR) and mortality using a restricted cubic splines regression model. Upper panel (A) includes the entire population enrolled in the study. Lower panel (B) includes only the younger half of the enrolled population (432 individuals, aged between 80 and 87 years). Graphs show hazard ratios (HR) for mortality according to SEVR adjusted for sex and age at enrollment in the study. Solid lines indicate HRs, and shadow shapes indicate 95% confidence intervals (CI).

(this value almost corresponds to the limit between the low and medium tertile). Further analyses were then performed by comparing the data referring to this SEVR threshold (Figure 2B). Non-linearity in the relationship between continuous measures of the SEVR and risk of mortality is shown in Figure 3. There was no difference in the male and female population (see Supplemental Material, Figures S3 and S4). No significant differences were shown stratifying SEVR tertiles separately into males and females (see Figure S5 in Supplemental Material).

According to the univariate analyses, the following variables were included in the multivariate Cox models: sex, age, body mass index (BMI), ADL, MMSE, and SEVR. Older age ($p < 0.001$), male sex ($p < 0.001$), low ADL scale score ($p < 0.001$), low BMI ($p = 0.002$) and low SEVR ($p = 0.005$) were independent determinants of 10-years total mortality (Figure S6A in Supplemental Material). A significant role of SEVR on total

mortality was observed in the medium- and long-term, at 4-, 6-, 8- and 10-year follow-up (p in multivariate analysis =0.009, 0.004, 0.003, and 0.015, respectively), on the contrary, no predictive value was observed on short-term mortality ($p = 0.302$ at 2-year follow-up) (see Table S2 in Supplemental Material).

Heart rate, mean pressure during the diastolic phase, and left ventricular ejection time were the determining factors of the SEVR with a significant predictive power on global mortality on a univariate analysis. However, only heart rate maintained its predictive power ($p = 0.028$) when these variables were included in a multivariate analysis together with sex, age, BMI, ADL, and MMSE ($p = 0.109$ for mean diastolic BP and $p = 0.114$ for left ventricular ejection time) (Figure S7).

A further analysis was performed on the younger half of the enrolled population (414 individuals, aged between 80 and 87 years). Figure S3 in Supplemental Material shows the survival curves for total mortality in this younger cohort. In the latter younger population, age and BMI did not represent a significant independent predictor of totamortality, while low SEVR ($p < 0.001$), male sex ($p < 0.001$), and low ADL ($p < 0.001$) were significantly associated with mortality (Figure S6B in Supplemental Material). In the older population over 87 years old, the predictive value of SEVR on medium- and long-term mortality is lost ($p = 704$) (see Supplemental Material, Figures S8 and S9).

A similar analysis was conducted using the SEVR as traditionally formulated on the basis of the simple relationship between the area below the diastolic phase and the systolic phase of the central pressure curve. No predictive power on the global mortality of this "traditional" SEVR was shown (Figures S10 and S11 in Supplemental Material).

DISCUSSION

Our study investigated the prognostic significance of estimating the imbalance between myocardial oxygen supply and demand in a population with a baseline age >80 years old living in nursing homes. This study provides three noteworthy results. First, higher SEVR values were associated with higher survival rates from the fourth up to the tenth year of follow-up. Second, the SEVR cutoff value of 83% was identified as the best predictor of total mortality. Third, in the prognostic assessment of total mortality, it may be worthwhile to use validated and accurate methods for the non-invasive estimation of the subendocardial oxygen supply and demand imbalance.

Low values of SEVR and total mortality

At the beginning of the 1970s G.D. Buckberg and J.I.E. Hoffman introduced a useful index to assess cardiac ischemic risk that reflects the relationship between subendocardial oxygen supply and demand, also known as the Buckberg index or SEVR. This index was defined by analyzing left ventricular and aortic pressure curves during invasive studies.[5,6,18]

Blood flow to subendocardial layers occurs during diastolic phase of the cardiac cycle, and, in the absence of coronary hemodynamically significant stenosis, the diastolic pressure in coronary arteries is equal to diastolic pressure in the ascending aorta. Thus, for a given heart rate, subendocardial perfusion largely depends on the coronary diastolic pressure. However, at the level of the subendocardial layer, perfusion is opposed by the intracavitary pressure of the left ventricle. Therefore, subendocardial coronary flow depends on the pressure gradient in diastole between the coronary artery intravascular pressure and left ventricular diastolic pressure. The area between the aortic and the left ventricular pressure curve in diastole (DPTI) can be considered a surrogate index of blood flow to the subendocardium.

An efficient and complex autoregulating mechanism ensures adequate myocardial perfusion in response to rapid and abrupt hemodynamic changes in the cardiovascular system by maintaining myocardial perfusion at constant levels, despite the changes in thrust pressure present in the ascending aorta and coronary arteries.[19,20] However, once autoregulation fails, a decreased perfusing pressure may not be compensated by coronary vasodilation, or increased myocardial oxygen requirements may not be compensated by an increase in flow, resulting in myocardial ischemia. Once the coronary flow reserve is exhausted, myocardial viability is warranted by the delicate balance between oxygen supply and needs in the subendocardium. This could be a condition that occurs in the frail older people and that would justify the results of the present study.

Oxygen consumption depends on myocardial work, and it is mainly affected by the afterload. The area under the aortic pressure curve in systole (SPTI), from the onset of ventricular systole to the dicrotic notch, can be considered an effective surrogate index of the left ventricular afterload and directly correlates with myocardial oxygen consumption.

The SEVR is a useful and effective index to describe the balance between cardiac blood flow supply (represented by DPTI) and demand (represented by SPTI).[5,21]

Aging-related stiffening of the large elastic arteries causes a decrease in diastolic BP and an increase in systolic BP in the aorta. The result is a decrease in the balance

between subendocardial oxygen supply and demand due to reduced subendocardial blood supply and increased ventricular afterload, respectively.[22]

In our study, reduced SEVR values were associated with an increase in total mortality with significant hazard ratios for mortality at 4, 6, 8, and 10 years, even in the model adjusted for important covariates as age, sex, BMI, MMSE, and ADL.

Considering the long follow-up period in relation to the advanced age of the population studied, a separate analysis was performed on the "younger" half of the participants, aged between 80 and 87 years. Unexpectedly, age as well as reduced BMI did not represent a significant prognostic factor for mortality in this population, while reduced SEVR values reinforced their negative prognostic power. Actually, the analysis of 10-year mortality data on the older population (over 87 years) can hardly be considered as meaningful, given the inescapably high mortality rate at this age.

Prognostic threshold value of SEVR

Another important goal of our study was to define the optimal cut-off value of SEVR to discriminate the total mortality risk in our cohort. A threshold equal to SEVR values of 83% was identified as the best predictor of mid and long-term mortality.

A number of studies showed that DPTI/SPTI ratio (SEVR) values below a critical level (threshold value identified in 45%) were associated with ongoing subendocardial ischemia,[23] even in the absence of hemodynamically significant coronary artery disease.[6,18,24] A DPTI / SPTI ratio below 45% is related to ischemic myocardial damage; our study has shown that SEVR values below 83% were associated with a worse prognosis on total mortality in the medium- and long-term. Starting from these results, we can therefore consider that older persons with SEVR values >83% (corresponding to the 33rd percentile in our population) can less easily reach a discrepancy between myocardial oxygen supply and demand in conditions of critical coronary flow (frail patients with reduced coronary reserve and inadequate autoregulation of coronary flow, or important fall in the diastolic perfusion pressure).

Non-invasive assessment of SEVR

The SEVR described in the 1970s by Buckberg and Hoffmann required invasive arterial catheterization, and this was a major limitation, which has restricted its application in clinical practice. With the advent of arterial applanation tonometry it has become possible to estimate the SEVR in a non-invasive way. The "traditional" method of estimating the SEVR totally ignores the role of left ventricular diastolic pressure,[25,26] isovolumic contraction, and isovolumic relaxation times. As the isovolumic contraction time/ejection time ratio increases significantly in patients with heart failure, the "traditional" tonometric method may overestimate the myocardial oxygen supply and demand ratio in these patients by even 80%–100% with regard to its real value.[16]

Limitations

The main limitation of the present study is represented by the difficulty in identifying the exact cause of death in this very old population. The majority of our population was over 90 at the time of death (average age 92.1 ± 4.9 years). At that age, except for selected cases in which a precise diagnosis of neoplastic disease was made, or in the presence of traumatic events (consequences of falls or syncopal episodes), in the vast majority of cases the cause of death was unknown and impossible to define correctly, being multifactorial or the result of progressive wasting or senile marasmus. In the majority of cases, death occurred in retirement homes. There were rare hospitalized cases in which it was possible to ascertain the causes of death. Moreover, the search for biological markers of fragility could have further clarified the results of the present study, but these data were not available. Because reliable information data regarding hospitalization was not available, this study is not able to assess relationship between SEVER and this important outcome in older persons. Another limitation is that our only measure of function and frailty status were ADL and MMSE assessment; therefore we are unable to determine if there is a correlation between our SEVER and frailty status or more robust measures of physical function. Moreover, the exclusion at the time of enrolment of patients with impaired autonomy (ADL <2/6) and with severe dementia (MMSE <12/30) may have created a possible bias in patient selection. We are aware that the results of our study cannot be necessarily extended to the entire population over 80 years of age, however, we believe that, despite these limitations, the results of our study can be considered as part of the clinical evaluation of the older population. Further studies are needed to extend the results of our study to the non-institutionalized population as well.

CONCLUSION

Low SEVR values, together with low ADL, and MMSE, strongly predict medium- and long-term mortality in the older population. Correct estimation of SEVR could help

in risk assessment and may improve diagnostic and therapeutic strategies in the older population, frail, and individuals subjected to polytherapy. Further studies are needed to confirm whether low SEVR values can be considered as a marker of "cardiovascular frailty".

AUTHOR CONTRIBUTIONS

A. Benetos and G. Parati have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: P. Salvi, A. Grillo, A.P. Avolio, G. Parati, A. Benetos. Drafting of the manuscript: P. Salvi, A. Grillo, L. Salvi, A.P. Avolio, G. Parati, A. Benetos. All authors contributed to data interpretation and critical review of the manuscript. Statistical analysis: A. Grillo, C. Labat. Obtained funding: P. Salvi, A. Benetos. Administrative, technical, or material support: S. Gautier, L. Salvi, C. Labat. Supervision: P. Salvi, B. Fabris, R. Carretta, A.P. Avolio, G. Parati, A. Benetos.

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CONFLICT OF INTEREST STATEMENT

Paolo Salvi has served as a consultant for DiaTecne srl. and Isabella Tan is an employee of ATCOR, CardieX. The remaining authors declare that there is no conflict of interest.

SPONSOR'S ROLE

Sponsors of the study had no role in the design, methods, data collection, analysis, or preparation of the paper.

ORCID

Paolo Salvi https://orcid.org/0000-0001-8663-5426
Andrea Grillo https://orcid.org/0000-0002-4455-4991
Carlos Labat https://orcid.org/0000-0002-5275-3405
Lucia Salvi https://orcid.org/0000-0002-7354-9366
Filippo Valbusa https://orcid.org/0000-0001-7527-6974
Isabella Tan https://orcid.org/0000-0003-3123-6190
Renzo Carretta https://orcid.org/0000-0001-6115-9953
Alberto P. Avolio https://orcid.org/0000-0002-8311-2010
Gianfranco Parati https://orcid.org/0000-0001-9402-7439
Athanase Benetos https://orcid.org/0000-0002-5197-1515

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SUPPORTING INFORMATION

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

Table S1. Clinical characteristics of the overall population with respect to sex.
Table S2. Relationships between subendocardial viability ratio (SEVR) and total mortality at the 2-, 4-, 6-, and 8-year follow-up assessed on both univariate (Model 1) and multivariate analyses (Model 2).
Figure S1. Subendocardial viability ratio (SEVR) values, in relation to the activity of daily living (ADL) score at the time of enrollment.
Figure S2. Subendocardial viability ratio (SEVR) values, in relation to the minimal mental state examination (MMSE) score at the time of enrollment.
Figure S3. Survival curves (Log-rank analysis) for total mortality in the half population aged 80 to 87 years for subendocardial viability ratio (SEVR) values above and below 83%.
Figure S4. Survival curves (log-rank analysis) for total mortality in females and males.
Figure S5. Survival curves (log-rank analysis) for total mortality according to the tertiles of subendocardial viability ratio (SEVR), stratifying SEVR tertiles separately into males and females.
Figure S6. Relationships between subendocardial viability ratio (SEVR) and total mortality assessed on both univariate and multivariate analyses.
Figure S7. Predictive power (Cox univariate analysis) on total mortality of the main haemodynamic parameters and factors determining subendocardial viability ratio (SEVR).
Figure S8. Relationships between subendocardial viability ratio (SEVR) and total mortality assessed on both univariate and multivariate analyses in the over 87 years population.
Figure S9. Survival curves (log-rank analyses) for total mortality according to subendocardial viability ratio (SEVR) values above and elbow 83% in the over 87 years population.
Figure S10. Survival curves (log-rank analyses) for total mortality according to the tertiles of subendocardial viability ratio (SEVR) assessed by "traditional" method.
Figure S11. Relationships between subendocardial viability ratio (SEVR) assessed by "traditional" method and total mortality assessed on both univariate and multivariate analyses.

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