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AORTIC VALVE REPLACEMENT IN ELDERLY SUBJECTS: EFFECTS ON PHYSICAL PERFORMANCE, COGNITIVE FUNCTION AND QUALITY OF LIFE

Coordinatore: Ch.mo Prof. Paolo Angeli

Supervisore: Ch.mo Prof. Enzo Manzato

Co-Supervisore: Dr Giuseppe Sergi

Dottorando: Marina De Rui

SUMMARY

RIASSUNTO

Premessa: la stenosi valvolare aortica (AVS) sta diventando sempre più frequente nella popolazione anziana, coinvolgendo circa il 13.2% dei soggetti sopra i 75 anni. Oltre a compromettere la qualità della vita, la AVS di grado severo non trattata porta alla morte in un tempo relativamente breve. La storia naturale della AVS può essere modificata dalla sostituzione della valvola aortica (AVR). I progressi nelle tecniche operatorie e anestesiologiche hanno ampliato negli ultimi anni l'accesso all'intervento chirurgico a pazienti sempre più anziani e sempre più fragili. In letteratura gli studi hanno finora valutato l'efficacia della AVR nel paziente anziano in termini di mortalità peri- e post-operatoria, mentre mancano dati circa l'esito dell'intervento sulla salute globale del paziente fragile a medio termine.

Scopo dello studio: lo scopo del nostro studio era valutare nel soggetto anziano l'impatto dell'intervento di AVR sulla performance fisica, sullo stato cognitivo e sulla qualità di vita a distanza di 45 giorni, tre e sei mesi dall'intervento chirurgico.

Soggetti e metodi: in collaborazione con l'U.O. Cardiochirurgia, secondo un disegno osservazionale longitudinale sono stati studiati 46 pazienti di età > 70 anni affetti da AVS per i quali era stata posta indicazione all'AVR. I soggetti sono stati valutati prima dell'intervento chirurgico (T0) e dopo l'intervento chirurgico a 45 giorni (T1), a tre mesi (T2) e a 6 mesi (T3). In tutte le visite i soggetti sono stati sottoposti a una valutazione geriatrica multidimensionale, comprensiva di esame clinico, valutazione dell'autonomia funzionale (*Activites of Daily Living e Instrumental Activites of Daily Living Scales*), dello stato cognitivo (*Mini Mental State Examination, Montreal Cognitive Assessment*), del tono dell'umore (*Geriatric Depression Scale*), della qualità di vita (*Short-Form 36 items Health Survey*, SF-36) e della performance fisica (*Short Physical Performance Battery, Gait*

Speed, Six minute Walking Test, misurazione della forza massimale degli arti superiori e inferiori).

Risultati: dei 46 pazienti inclusi nello studio in questo lavoro sono stati considerati solo i 22 soggetti che hanno completato il follow-up a 6 mesi. Rispetto alla valutazione preoperatoria, al follow-up dei 45 giorni era evidente un significativo peggioramento nei parametri nutrizionali (BMI,circonferenza del braccio, punteggio MNA) e dei test di performance fisica (forza massimale di prensione della mano, forza di flesso-estensione degli arti inferiori e test isometrico della forza degli arti inferiori). Al follow-up dei 6 mesi MNA, MMSE, MoCA, SPPB miglioravano significativamente, raggiungendo valori superiori a quelli basali. La forza degli arti superiori e inferiori non si modificava significativamente 6 mesi dopo l'intervento rispetto al basale. Per ciò che concerne la qualità di vita, i punteggi all'SF-36 rimanevano pressoché stabili a 45 giorni mentre miglioravano significativamente al controllo a 3 e a 6 mesi.

Considerando la variazione della velocità del passo tra la valutazione basale e quella a 6 mesi, i soggetti che presentavano un miglioramento nel follow up, rispetto agli altri soggetti al basale presentavano valori più bassi di forza degli arti superiori e inferiori, di velocità del passo e percorrevano una distanza significativamente inferiore al 6-MWT.

Conclusioni: i dati di questo studio evidenziano che nei pazienti anziani affetti da AVS, la sostituzione valvolare aortica migliora lo stato nutrizionale, le facoltà cognitive, il tono dell'umore, la performance fisica e la qualità di vita. La forza degli arti inferiori e superiori invece mantiene a 6 mesi valori non diversi da quelli pre-operatori. I soggetti che sembrano beneficiare maggiormente dal punto di vista funzionale della AVR sono quelli più compromessi a basale dal punto di vista della performance fisica.

ABSTRACT

Background: aortic valve stenosis (AVS) is becoming more and more common in the elderly population, involving around 13.2% of subjects older than 75 years. In addition to worsening quality of life, untreated severe AVS has been associated with high short term mortality rate. However, these adverse outcomes could be modified by aortic valve replacement (AVR). In recent years, in particular, newer surgery procedures and anesthesiological techniques have allowed also older and frailer patients access to AVR procedures. Previous studies have evaluated the effectiveness of AVR in older subjects in terms of peri- and post-operative mortality, but its impact on frail patients' global health has been scarcely investigated.

Aim of the study: the aim of our study was to evaluate the impact of AVR procedure on older patients' physical performance, cognitive status and quality of life at 45 days, three and six months after surgery.

Subjects and methods: this prospective study included 46 patients over 70 years, enrolled in collaboration with the Department of Cardiac Surgery of the University of Padova. All subjects were affected by AVS, and were recommended to undergo AVR. Study participants were evaluated with a multidimensional geriatric assessment before AVR (T0) and 45 days (T1), three (T2) and six months (T3) after surgery. In particular, for each participant we collected data on clinical examination, self-sufficiency (using the Activites of Daily Living and Instrumental Activites of Daily Living scales), cognitive status (using the Mini Mental State Examination and the Montreal Cognitive Assessment), presence of depressive symptom (through the Geriatric Depression Scale), quality of life (using the Short-Form 36 items Health Survey) and physical performance (through the Short Physical

Performance Battery, gait speed, 6-minute walking test, and measurements of upper and lower limbs strength).

Results: of the initial sample of 46 patients, 22 reached the 6-month follow-up and were included in the study. Compared with the pre-operative evaluation, at T1 we observed a significant decline in nutritional status (BMI, arm circumference, MNA score) and in physical performance (SPPB, handgrip strength, lower limb flexion-extension and isometric strength). At T3, MMSE, MoCA, MNA and SPPB scores improved significantly from baseline. Upper and lower limbs strength at 6-month follow up was not significantly different from baseline. Quality of life remained nearly stable at T1, but improved significantly at T2 and T3.

Considering the variation in gait speed from baseline to 6-month follow up, subjects that showed an improvement in this item compared to worsening subjects, at baseline had lower values of handgrip and limbs strength, gait speed and 6-MWT distance.

Conclusions: our results show that in older AVS patients, AVR have a positive impact on nutrition, physical performance, cognitive functioning, mood and quality of life, whereas it does not have any significant impact on limbs muscle strength.

INTRODUCTION

The elderly population is the fastest growing demographic in Western countries, with the world population of people over the age of 60 years expected to double to 2 billion by the year 2015 and those over the age of 80 years to increase 26-fold (1).

As the population ages, the incidence of age-related comorbidities as diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, renal disease, cerebrovascular disease, and cardiovascular disease increases.

Cardiovascular disease occur in approximately one-quarter of the population over the age of 75 years. Also the prevalence of valvular heart disease (VHD) increases with age, with aortic valve stenosis (AVS) and mitral regurgitation being the most prevalent valvular disorders in the elderly (2,3). Population-based studies report that age-adjusted prevalence of moderate or severe AVS is about 2.5%, with a significant influence by age: $<2\%$ prevalence in those <65 years of age and 13.2% in those ≥ 75 years of age (3,4).

Pathophysiology of AVS

The pathophysiology of degenerative calcific aortic stenosis is the result of a biologically active process with characteristic features of an osteoblast phenotype (5). Risk factors for disease progression mirror those of coronary artery disease, with risk factors including hypertension, hyperlipidemia, diabetes, smoking, and renal dysfunction. An inflammatory basis for aortic stenosis is supported by studies demonstrating increasing 18-fluorodeoxyglucose levels, which is a marker of macrophage activity, with increasing valve stenosis severity (6).

An increase in the aortic valve gradient results in pressure overload and concentric left ventricular hypertrophy with preservation of left ventricular cavity size and ejection-fraction. Nevertheless, the hypertrophy and associated fibrosis (7) contribute to left ventricular diastolic dysfunction and increased filling pressures.

Symptoms of AVS

The three cardinal symptoms of aortic stenosis indicating a need for intervention are angina, exertional syncope or presyncope, and heart failure (e.g. exertional cardiac dyspnoea, orthopnea, paroxysmal nocturnal dyspnoea, pedal oedema).

Angina is the result of increased myocardial muscle and increased myocardial demand with limited blood supply with or without coronary artery disease. Exertional angina may be present in up to 50% of patients with aortic stenosis despite the absence of obstructive coronary artery disease (8). Exertional syncope or presyncope is the result of peripheral vasodilation with an inability of the heart to increase stroke volume due to the obstruction in left ventricular outflow. Finally, heart failure is the result of left ventricular hypertrophy with fibrosis and diastolic dysfunction, with increased filling pressure, often despite preserved left ventricular ejection fraction (7).

Criteria for climatically significant AVS

The normal aortic valve has three thin highly mobile leaflets that provide a valve opening of 3 to 4 cm^2 and minimal gradient (<10 mmHg). Progression of aortic stenosis in the early stages is very slow with estimates of lumen loss of 0.10 cm^2 per year (9) and increase in peak gradient of 10 mmHg per year (10), but there is a great variation among individual patients. There is considerable valve area reserve. Symptoms of aortic stenosis do not develop until there has been 60% to 75% loss of valve area to less than 1.0 cm^2. As a result, many patients remain asymptomatic for decades, with the symptoms of dyspnoea, angina and syncope to occur in the sixth to eighth decade of life (11). In older people these symptoms result in disability, recurrent hospitalizations, impairment in quality of life, and finally death.

Measurement of AVS

Resting thranstoracic echocardiography readily allows for assessment of left ventricular wall thickness, cavity size, and regional-global systolic function. In addition, aortic valve morphology can be assessed. Finally, Doppler echocardiography allows for an accurate noninvasive assessment of aortic valve peak and mean gradients, estimation of aortic valve area, and assessment of aortic regurgitation. The transthoracic echocardiography peak aortic valve gradient is slightly higher than the gradient reported at cardiac catheterization as it measures the maximal instantaneous peak gradient between the aorta and the left ventricle, while invasive measurements report the difference between the peak left ventricular pressure and the peak aortic pressure. The mean gradients derived by both methods are similar.

If Doppler echocardiography is unable to assess the valve, other options include planimetry using 2- or 3- dimensional transesophageal echocardiography, computed tomography, and cardiovascular magnetic resonance. All of these methods offer good correlation with thranstoracic echocardiography and cardiac catheterization but with additional costs, invasiveness, or radiation exposure.

Because the presence of angina may be related to aortic stenosis or coexistent coronary artery disease and because patients with aortic stenosis often have typical risk factors for coronary artery disease, screening coronary angiography is recommended for most adult patients prior to aortic valve surgery (12,13).

Management of significant AVS

Medical therapies for degenerative VHD primarily consist in symptom control but they have with little effect on mortality, with 2-year mortality following the onset of symptoms as high as 80% (14). Aortic valve replacement therapy is the only treatment that has proved helpful in strengthening the survival prospects of these patients (15), with 3-year survival following surgery of 87% (14).

Class I indications for aortic valve surgery as recommended by both the ACC/AHA and the European Society of Cardiology and European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines (12,13) include symptomatic patients with severe aortic stenosis (aortic valve area <1.0 cm^2 or indexed aortic valve area, i.e. aortic valve area divided by body surface area, <0.6 cm^2/m^2) and asymptomatic patients with depressed ejection fraction (<50%).

Of the three cardinal symptoms, heart failure is the most ominous with survival of less than a year after heart failure symptoms without valve replacement; for patients who present with exertional syncope, survival is less than two years after the development of symptoms without valve replacement (16).

PREMISE OF THE STUDY

Aortic valve stenosis (AVS) is becoming more and more common in the elderly population, involving around 13.2% of subjects older than 75 years. The prevalence of valvular heart disease (VHD) increases with age, with aortic valve stenosis (AVS) and mitral regurgitation being the most prevalent valvular disorders in the elderly (2-4).

AVS remains asymptomatic for decades, with the symptoms of dyspnoea, angina and syncope to occur in the sixth to eighth decade of life (11). In older people these symptoms can result in disability, recurrent hospitalizations, impairment in quality of life, and finally death. These adverse outcomes could be modified by the aortic valve replacement (AVR). In recent years, in particular, surgery procedures and anesthesiological techniques have allowed also older and frailer patients access to AVR procedures.

In the elderly, AVR is associated with significant morbidity and mortality due to the global complexity (or frailty) of this class of patients (17). Frailty is characterized by impaired physiologic response and decreased resistance to stressors, due to a lack of physiological reserves across multiple organ systems. The assessment of frailty requires the evaluation of different domains, including physical function (for example, evaluating standing balance, gait speed, the distance covered by the subject walking for 5 or 6 minutes), neuropsychological and nutritional status, and social factors.

Physical performance and frailty are predictors of disability and mortality (18-24), also in relation to cardiac surgery in elderly patients (25). Furthermore, the relevance of performance in the elderly is highlighted also by the fact that including a functional parameter as gait speed to the STS score in patients undergoing cardiac surgery, improved 2- to 3-fold risk prediction of in-hospital morbidity and mortality (26).

Hence frailty can be used to identify subjects at greater risk for perioperative complications and mortality. Nevertheless, since that AVS itself can be a cause of disability, frailty and poor quality of life in elderly patients, the correction of valvular defect may modify and improve performance status in older patients, which is also the aim of AVR. Consequently, the evaluation of AVR outcomes in older adults, besides the improvement of echocardiographic parameters, should include also the assessment of changes in physical performance, in neurospichological and functional status, as well as in quality of life.

Up to now, several studies have evaluated the effectiveness of AVR in older subjects in terms of peri- and post-operative mortality (26,27), but its impact on physical and mental performance and global health has been scarcely investigated.

We hypothesized that aortic valve replacement would worsen cognitive function in elderly patients due to anaesthesia, surgery and hospitalization. Moreover, that AVR could improve functional performance and quality of life in the medium-term.

AIMS OF THE STUDY

The aim of the present study was to assess the effects of AVR in elderly patients in relation to physical performance, cognition, and quality of life in the short- and medium term. Moreover, to assess the impact of pre-operatory functional status on physical performance.

SUBJECTS AND METHODS

This observational prospective study was designed and conducted in collaboration between the Department of Medicine - Geriatric Section and the Cardiac Surgery Department of Padova University.

Caucasian subjects aged >70 years affected by severe or symptomatic aortic valve stenosis with indication for isolated aortic valve replacement were recruited in the study. Subjects were not included only if they did not give their consent to participate to the study.

The study was designed in accordance with the Helsinki Declaration. All participants were fully informed about the nature, purpose, procedures, and risks of the study and gave their informed consent.

As illustrated in the flow chart (Figure 1), among 56 patients affected by AVS with indication for isolated valve replacement who referred to the Cardiac Surgery Department between January 2017 and August 2018, 10 refused to participate to the study, so 46 subjects were enrolled in the study. For the present analysis we selected only patients who completed the 6-month follow up, so the considered sample is composed of 22 participants.

All subjects underwent sternotomic AVS.

Subjects were evaluated by trained medical personnel before surgery (T0) and after VRS at 45 days, 3 and 6 months (T1, T2, T3 visits, respectively).

At each visit patients underwent a global clinical assessment and the following evaluations:

- anthropometric measurements: body weight and stature were measured to the nearest 0.1 kg and 0.1 cm with a standard balance and stadiometer (Seca; Germany) with subjects wearing light clothing and no shoes. Their BMI was calculated as their weight in kilograms divided by the square of their stature in meters.

Circumferences were measured using a non-elastic but flexible plastic tape. Waist circumference was measured at the level of midway between the lowest rib and the top of the iliac crest. Mid-upper-arm circumference was measured using a flexible tape at the midway between the olecranon and acromial process on the upper right arm. Calf circumference was measured on the left leg in a sitting position with the knee and ankle at a right angle and feet resting on the floor. The calf circumference was measured at the point of greatest circumference. Subcutaneous tissues were not compressed;

- comorbidities and indicators of disease severity: comorbidity was assessed using the Cumulative Illness Rating Scale (CIRS) (28), a validated physician-rated index calculated by collecting the subject's medical history as well as conducting a physical examination and performing laboratory tests. The CIRS classifies comorbidities among 13 organ systems and grades each condition from 0 (no problem) to 4 (severely incapacitating or life-threatening conditions). The comorbidity index (CIRS-CI) is given by the number of conditions graded as ≥ 3. The severity index (CIRS-SI) is the mean of the severity scores for each of the 13 organ systems;
- cognitive evaluation using:
    - Mini-Mental State Examination (MMSE) (29), a validated neuropsychological tool for measuring global cognitive function with orientation, concentration, language, praxis, and memory components. Total scores range from 0 (worst performance) and 30 (best performance). Crude MMSE scores obtained in our sample were adjusted for age and formal

education using coefficients proposed for the Italian population (30). Adjusted scores > 24 indicated a normal cognitive function (31);

  - Montreal Cognitive Assessment (MoCA) (32), a simple 10-min paper-and-pencil test with a maximum score of 30. It assesses multiple cognitive domains including memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration, and orientation. A score ≥26 is considered normal;

- affective status by means of the Geriatric Depression Scale (GDS) (33, a 30-item self-reporting tool for identifying depression that has been validated for use in the elderly. Scores <10 indicate absence of depression, scores 11-16 indicate a mild to moderate depression, and scores >17 indicate severe depression;
- functional evaluation based on Activities of Daily Living (ADL) (34) and Instrumental Activities of Daily Living (IADL) (35) indexes. Given the traditionally different role of genders in Italian families, 3 items (preparing meals, doing housework, and doing laundry) were not applied to men. To make the values comparable, the IADL scores were calculated as percentages of the maximum value;
- nutritional status was evaluated with the Mini-Nutritional Assessment (MNA) tool (36), an internationally validated method consisting of 18 items covering anthropometric measures, health status, dietary patterns, and subjective assessments of the participant's nutritional and health status. A total score ≥ 23.5 distinguishes people with a good nutritional status from those at nutritional risk (MNA score between 17 and 23.5) and those with protein calorie malnutrition (MNA score < 17);

- quality of life by means of the Short-Form 36 items health Survey (SF-36) (37), a test that comprises 36 multiple choice questions sorted into 8 subscales that describe overall health status. These subscales are physical functioning (PF), role limitations as a result of physical problems (RP), bodily pain (BP), general health perception (GH), vitality (the frequency of feeling full of energy vs feeling tired) (VT), social functioning (SF), role limitations resulting from emotional problems (RE), and general mental health (MH). Low numeric scores reflect a perception of poor health, loss of function, and presence of pain. High numeric scores reflect a perception of good health, no functional deficits, and absence of pain. SF-36 items were coded and scored as outlined in the SF-36 scoring manual and a score >50 for each item was considered as indicative of a "sufficiently" good perceived health status (38);
- physical performance using:
    - Short Physical Performance Battery (SPPB) (39), which consists of 3 objective physical function tests: 4-meter gait speed, repeated chair stands, and standing balance in increasingly challenging positions. Walking speed was calculated as the best performance achieved in two walks at the participant's usual pace along a corridor 4-meter long. For the chair stands test, the participants were asked to rise 5 times from a seated position as quickly as possible with their hands folded across their chest. For the standing balance tests, participants were asked to stand in three increasingly difficult positions (with their feet side by side and in semitandem and full-tandem positions) for 10 seconds each. Each test was scored from 0 (worst)

to 4 (best), and the scores from all three tests were combined to obtain a composite score of 0 to 12. Higher scores reflect better physical function;

- 6-minute walking test (6-MWT) (40): participants were asked to walk at their usual pace for 6 minutes, and the distance they covered was recorded in meters. In evaluating changes in 6-MWT a threshold of 54 meters was considered as representative of clinically significant change;
- measurement of handgrip strength on the dominant side by using DynEx electronic hand dynamometers. The participants were seated in a standard armchair with their shoulder adducted and neutrally rotated, their elbow flexed at 90°, and their forearm and wrist in a natural position. They were asked to grip the dynamometer smoothly, progressing up to their maximal strength in response to a voice command, without any wrenching or jerking motion. Three measurements were obtained on the dominant side with a 1-minute rest between trials, and the highest measurement was used in our analyses. The handgrip endurance was determined by asking the subject to maintain 50% of maximal voluntary contraction for as long as he/she could and the time was recorded in seconds by using a stop watch (41);
- measurement of isometric knee extension torque and isokinetic (flexion and extension) strength on the dominant side by using the dynamometer chair (Easytech s.r.l.). The participants were positioned upright with straps to fix their hips to the chair. For each of the 3 measurements, participants were asked to reach their maximal voluntary contraction. Three to five seconds after reaching their maximum effort, they were asked to stop the contraction. Each measurement was repeated three times, and patients

rested for 2 to 3 minutes between trials. The highest-peak torque (PT) was used for the analysis.

Statistical analysis

All measurements obtained at baseline and follow-up were used in the data analysis. Participants' characteristics were summarized using mean ± standard deviation for continuous variables and counts and percentages for categorical variables. For continuous variables, normal distributions were tested using the Shapiro-Wilk test. The non-parametric Mann-Whitney test was used to check differences between medians of SPPB scores.

Baseline characteristics were compared between genders by using independent t-tests, chi-square tests, or Fisher's exact test, as appropriate. Paired t-tests were used for within-group comparisons of baseline and follow up data.

To assess which baseline characteristics were associated with a better global outcome 6 months after surgery, we calculated a variable, *Δ gate speed*, obtained from T3 gate speed minus T0 gate speed. Furthermore, the variable *Δ gate speed* was dichotomized into > 0 (indicating an improvement in gate speed at 6-month follow up *vs* baseline) and < 0 (indicating a worsening). Pearson's correlation coefficient (r) was applied to measure simple linear associations between *Δ gate speed* and baseline characteristics of the subjects.

All analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p value <0.05.

RESULTS

Baseline characteristics of the sample

General characteristics of the sample grouped by sex are reported in Table 1. Men represented 54% of the study population. Men and women did not differ for BMI nor for echocardiographic parameters. The majority of both men and women was in NYHA class 2, whether approximately 25% of them was in NYHA class 3. Angina and syncope were more prevalent in women but the difference did not reach statistical significance.

Figure 2 illustrates the prevalence of comorbidities in the population sample. All women had hypertension and 88.8% of them had also dyslipidemia, whereas in men the prevalence of hypertension and dyslipidemia was 66.6% and 41.6%, respectively. Diabetes, atrial fibrillation and cerebrovascular diseases were more prevalent in men, whereas coronary heart disease and COPD were found more frequently in women. Nevertheless, these differences were not statistically significant.

Regarding multidimensional assessment, CIRS-CI and CIRS-SI scores were significantly higher in women (4.5±0.9 and 1.9±0.2, respectively) than in men (3.5±1.1 and 1.7±0.1, respectively). MNA score was not significantly different between genders, but 33% of women and 8.3% of men were at risk of malnutrition (MNA score 17-23.5).

MMSE score was not different between genders, with 1 woman and 1 man having a MMSE score < 24/30. MoCA score was significantly lower in women than men (21.5±4.4 vs 24.9±2.3 respectively, p 0.041), with 88.9% of women and 45.5% of men having a MoCA score <26.

GDS mean score was not significantly different in the two groups, but 63.6% of men and 33.3% of women had a mild-to-moderate depression (GDS score 11-16), and 22.2% of women had a severe depression (GDS score >17).

ADL and IADL scores comparable between genders.

Regarding physical performance tests, women covered a significantly lower distance compared with men (301.3±124.4 meters vs 442.9±71.7 meters, respectively, p = 0.004), and had lower values lower limbs performance and handgrip strength (21.3±7.2 Kg in women vs 42.8±9.8 Kg in men, p < 0.0001).

Regarding quality of life, as showed in Figure 3, SF36 scores exploring physical functioning were higher in men (70.0±17.8 in men vs 48.3±29.1 in women, p 0.05), as well as scores related to physical role functioning (51.0±28.1 in men vs 28.9±35.0 in women, p = 0.01) and bodily pain (71.9±18.3 in men vs 48.4±11.8 in women, p = 0.004). In four SF36 items (physical functioning, bodily pain, emotional role functioning and mental health) the majority of subjects had a score > 50 (Figure 5).

Comparison between baseline and 45-day follow up

As reported in Table 2, 45 days after surgery subjects showed a significant worsening regarding nutritional aspects. Body weight decreased significantly (76.6±10.3 vs 73.9±0.8 Kg, p 0.001), as well as arm circumference (28.5±3.4 vs 27.0±2.8 cm, p 0.014) and MNA score (25.0±1.8 vs 23.4±2.5, p 0.028). Calf and waist circumference did not change significantly.

No variations were seen in cognitive function (MMSE, MoCA, GDS scores) and in functional status (ADL and IADL scores).

Physical performance as explored by gait speed did not change significantly. During the 6-MWT subjects covered a significantly lower distance compared to baseline (p 0.05), and among SPPB items, standing balance score decreased significantly compared to baseline (p 0.05). Subjects with SPPB total score ≤8 increased from 9.5% to 21.1% (p 0.035).

Hangdrip maximal strength decreased significantly at 45-day follow up (33.7±14.4 vs 29.9±11.1 Kg, p 0.008), as well as peak-torque extension (73.7±30.7 vs 65.2±30.4 Nm, p 0.035), peak-torque flexion (32.1±15.1 vs 26.3±9.9 Nm, p 0.05) and isometric maximal strength (115.0±47.4 vs 97.9±39.0 Nm, p 0.001).

Regarding quality of life measured by SF36 (Figure 4), physical functioning (60.6±26.2 vs 51.5±19.8, p 0.043) and general health perceptions (60.0±20.7 and 49.9±17.0, p 0.05) worsened significantly.

Comparison between baseline and 3-month follow up

At 3-month follow up nutritional status was not significantly different from baseline (BMI, arm circumference, MNA score), as well as handgrip maximal strength, peak-torque extension and flexion. Isometric maximal strength was significantly lower than baseline 3 months after surgery (101.3±45.9 vs 115.0±47.4 Nm, p 0.007). Also repeated chair stands score was significantly higher at 3-month compared to baseline (p 0.05).

Mean GDS score did not change significantly, but the percentage of subjects with GDS score between 11 and 16 decreased significantly (40% vs 50%, p 0.05).

Regarding quality of life (Figure 4), mental health score increased significantly (53.1±18.3 vs 66.8±16.1, p 0.02).

Comparison between baseline and 6-month follow up

As reported in Table 2, at 6-month follow up BMI and anthropometric measurements (arm, calf and waist circumferences) were not different from baseline. MNA score increased significantly (25.0±1.8 vs 26.6±0.2, p 0.006).

Regarding cognition, both MMSE and MoCA scores increased significantly (for MMSE score: 26.6±2.2 vs 27.9±1.6, p 0.04; for MoCA score: 22.9±4.2 vs 25.0±2.4, p 0.016). GDS score was stable during follow up, but the percentage of subjects with GDS score between 11 and 16 decreased significantly (23.9% vs 50%, p 0.038).

Regarding functional status, the percentage of independent IADL increased at 6-month follow up (96.9±6.2 vs 98.2±12.4, p 0.004).

Considering SPPB test, repeated chair stand score and SPPB total score increased significantly from baseline (p 0.05, p 0.05, and p 0.028, respectively). The percentage of subjects with SPPB total score ≤8 decreased significantly (4.8% vs 9.5%, p 0.025). Gait speed increased significantly (1.10±0.09 vs 0.94±0.23 m/s, p 0.05).

At the 6-MWT the distance covered by subjects was not significantly different from baseline.

The strength of arms and limbs was not different at follow up.

Regarding quality of life (Figure 4), among SF36 items, physical role functioning score increased significantly (33.0±23.3 vs 63.1±21.1, p<0.0001), as well as vitality score (53.0±16.9 vs 63.5±17.6, p 0.013) and mental health score (53.1±18.3 vs 70.5±15.5, p 0.001). In all SF36 items the majority of subjects had a score >50 (Figure 5). Compared to baseline, the prevalence of subjects with satisfactory scores was significantly higher than baseline in physical role functioning, vitality, social role functioning and mental health (Figure 5).

Correlations between Δ gate speed and baseline characteristics of subjects

As evidenced in Figure 6, a significant inverse relationship emerged between Δ gate speed and baseline peak torque extension (r: -0.789, p 0 0.007) as well as between Δ gate speed and baseline handgrip endurance 50% (r: -0.651, p = 0.042).

Figure 7 shows the mean values of peak torque extension and handgrip endurance in the sample divided by improvement or worsening in gate speed 6 months after surgery compared to baseline. Both parameters are significantly different at baseline between the two groups ($p < 0.01$). Peak torque extension values remained lower through the whole study in the group with Δ gate speed > 0 compared to the other subgroup. Regarding handgrip endurance, the group of patients with Δ gate speed > 0 had a significantly lower value at baseline compared to the other group, but at 6-month assessment their mean value was higher than the other subjects, even if not significantly different.

As reported in Figure 7, also gait speed and 6-MWT distance at baseline were significantly lower in subjects with Δ gate speed > 0. At 6-month follow up this difference is nullified because of increasing results for the group with Δ gate speed > 0 and worsening results for subjects with Δ gate speed < 0.

DISCUSSION

The present study explores the short- and medium-term impact of AVR on functional and neuropsychological status in elderly patients. Our data suggest that aortic valve replacement leads to an improvement in patients' nutritional, neuropsychological and functional status and in perceived quality of life, whereas it does not have any significant impact on limbs muscle strength.

In our sample, the majority of subjects was in NYHA II class, having slight limitation of physical activity due to dyspnoea, whereas about a fourth of them had a marked limitation of physical activity (NYHA class III). Angina and syncope were not highly prevalent in the study population.

Echocardiography showed that all subjects had a normal left ventricle ejection fraction.

Comorbidities more frequently associated with aortic valve stenosis were hypertension, dyslipidemia, diabetes, and atrial fibrillation, with a prevalence similar to that reported in other studies (42,43). Women had a significantly higher comorbidity burden compared to men, as evidenced by CIRS-CI and CIRS-SI scores, in accordance also with previous studies (44,45).

From a nutritional point of view, subjects at baseline had a mean BMI of 28.4±4.3 Kg/m^2, indicative of normal weight – overweight. Nobody was underweight. Also mean MNA score was indicative of a normal nutritional status at baseline, but 28.6% of subjects were at risk for malnutrition (MNA score 17-23.5). These data are in line with those of Goldfarb et al. (46) who found 32.8% of subjects at risk for malnutrition among patients aged ≥70 years who underwent AVR. Actually they found also 8.7% of malnourished patients, but in the study included not only subjects who underwent surgical AVR but also transcatheter AVR (TAVR), an option dedicated to high risk patients who would be otherwise excluded from surgical AVR. Among patients undergoing general surgery, malnutrition is associated with delayed wound healing, postoperative complications, prolonged hospital length of stay, hospital readmission, and death (47,48). Regarding AVR, Goldfarb et al. (46) demonstrated that malnourished patients had a 3-fold higher crude risk of 1-year mortality compared with those with normal nutritional status. Furthermore, Chermesh et al. (49) found that incorporation of the nutritional assessment in the EuroSCORE significantly improved prediction of postoperative complications and in-hospital and 30-day mortality, compared with the EuroSCORE alone.

Surgical intervention had a great impact on nutritional status of our elderly subjects. At 45-day follow up, body weight decreased by 2.6±2.0 Kg and the proportion of subjects at risk for malnutrition almost doubled (52.6%). This weight loss is probably due to a reduction in calorie intake and hypermetabolism, as demonstrated also by Sallè et al. (50). In our sample, this worsening was reversible. In fact, at 3-month assessment body weight, BMI, MNA score and the percentage of subjects at risk for malnutrition were not different from baseline. Moreover, at 6-month follow up MNA score increased significantly and nobody was at risk for malnutrition.

To explore cognitive status we used two tests, MMSE and MoCA, since that the latter is more sensitive to subtle cognitive deficits than MMSE (51). In fact, according to MMSE score, almost all subjects were considered to have a normal cognition, while MoCA detected impaired cognition in 80% of the sample at baseline.

Since that AVR requires general anaesthesia, our preliminary hypothesis was that surgical intervention, in addition to hospitalization, could worsen cognitive performance in elderly subjects. Actually it was not like that. Not only MMSE and MoCA scores did not decrease at 45-day follow up, but they improved significantly at 6-month assessment compared to baseline. Also Knipp et al. (52), who studied 64 elderly patients with aortic stenosis undergoing aortic valve replacement, found that surgical intervention did not significantly change neuropsychological tests scores between baseline and 3-months.

Regarding mood, mean GDS score at baseline was 12.4±3.4, indicative of mild-to-moderate depression (GDS 11-16). Fifty percent of subjects had a score between 11 and 16, and 10% resulted as severely depressed. Immediately after surgery the prevalence of depressed subjects increased, but at 6-month follow up patients with mild-to moderate depression halved, whereas those with severe depression maintained proportionally stable.

Among physical performance tests, in our sample baseline SPPB score was 11 (interquartile range 8-12). Despite a very high score, 9.5% of subjects at baseline had an SPPB total score ≤8, the cut off commonly used for the diagnosis of sarcopenia (53). Immediately after surgery, the proportion of subjects with an SPPB score ≤8 increased significantly to 21.1% but at 6-month follow up decreased to 4.8%, which was significantly lower than baseline. Also repeated chair stands score and 4-meter gait speed at 6 months were better than before surgery. This functional improvement in the medium-term after AVR is particularly interesting since that SPPB test is considered a nonspecific but highly sensitive indicator of global health status (54). Moreover, this test has a strong and independent ability to predict mortality, morbidity and hospitalization in older adults (53,55), so an improvement in SPPB score may lead in the long term to a better capability of patients to react to future stressors.

The observed transient worsening in standing balance at 45 days after surgery may be an early consequence of deconditioning and muscle atrophy due to surgery and bed rest, which leads to muscle atrophy preferentially involving the anti-gravity muscle groups which are very important for posture (56,57).

Regarding gait speed, it is recognized as a valuable predictor for the onset of adverse health events (severe mobility limitation, mortality) in community-living elderly people (53), but also in patients undergoing cardiac surgery (26). Its importance has also been highlighted by the American College of Cardiology, which recommends that gate speed test be used to assess frailty and physical functioning when determining a patient’s suitability for transcatheter AVR (27). Considering the recognized importance of this indicator of global health status, we chose to examine 6-month variations in gait speed in relation to baseline characteristics of patients. We found that *Δ gate speed* was inversely correlated with basal peak torque extension and with baseline handgrip endurance (Figure 6). In other words, subjects with a basal lower level of physical performance were those who had a greater benefit in terms of gaining gait speed after AVR. Successively, we divided the sample in two groups depending on the presence of improvement or worsening in gait speed. We found that subjects who improved in gait speed, at baseline had a globally worse performance (Figure 7): in fact, they had lower baseline values of peak torque extension, handgrip endurance, gait speed and 6-MWT. Moreover, subjects who improved in gait speed, improved also in handgrip endurance and 6-MWT. To our knowledge, up to now, only Kotajarvi et al. (58) evaluated the effect of AVR on physical performance. They studied 103 elderly subjects using self-reported measures of functional capacity and found that 3 months after surgery patients with a greater improvement were those with a lower performance at baseline. These results evidence that pre-operatory assessment should not exclude a priori subjects with a worse physical performance, since that they could be the ones who have a greater global health benefit from AVR.

In the assessment of waking ability, the 6-MWT differs from gait speed in that provides a global assessment of endurance capacity (59), being influenced not only by musculoskeletal factors but also by cardiopulmonary compliance. In our sample, 6-MWT did not show any significant variation between baseline and 6-month follow up. However, 25% of subjects at 6-month visit had an improvement > 54 meters, which is commonly considered as clinically significant. The fact that only 25% of patients showed a clinically significant improvement in 6-MWT is due to the high mean performance at baseline. In fact, the group of patients who did not improve in 6-MWT, compared to patients who improve, at baseline covered a significantly higher distance (400.1±90.0 m vs 298.4±98.2 m, respectively; p 0.038).

Regarding upper and lower limbs strength, muscle function is important in the elderly: low levels of muscle strength in fact are significantly associated with various negative outcomes in older people, such as falls, fractures, functional limitations in activities of daily living, and death (60-65). Baseline values of our sample were comparable with those of the general population (66-69). At the first follow up visit upper and lower limbs strength significantly reduced as a consequence of surgery and bed rest, but at 3- and 6-month control they were not different from baseline. Hence, the improvement in functional performance after AVR evidenced by SPPB and gait speed is not related to the improvement in muscle strength, but it reflects a better global health status.

Finally, regarding quality of life (QoL), at baseline the majority of subjects had a score < 50 in four SF36 items. Immediately after surgery perceived QoL decreased in nearly all domains, but at subsequent visits al the scores improved and at 6 month scores were higher than baseline. As reported in Figure 5, six months after surgery the percentage of subjects with SF36 items scores > 50 increased, and the majority of subjects had a sufficient perceived QoL in all SF36 items. In particular, the improvement was significant for physical role functioning (i.e. problems encountered with daily activities or work as a result of physical health), vitality (i.e. a general measure of energy/fatigue), social role functioning (i.e. the ability to perform social activities in lieu of health problem) and mental health (i.e. the emotional, cognitive and intellectual status of the patient). Postoperative health-related QoL is a primary goal of surgery in the elderly and an important aspect for many patients in their decision-making. The challenge of surgery in this population is to provide a good QoL in the mid- to long-term (70,71). Shan et al. (72) performed a systematic review on the QoL benefits after AVR and found that elderly patients improve in QoL scores after surgery compared to baseline, and have equal or better QoL compared with an age-matched population.

The present study has some limitations. First of all, the number of subjects that completed the 6-month follow up is restricted so the results should be confirmed after increasing the sample size. Secondly, due to the very low mortality rate (only one person), we are unable to assess possible associations between baseline performance status and mortality. Actually, a low mortality rate is a positive outcome. Moreover, all patients underwent median sternotomy, so we do not have a comparison group treated with transcatheter aortic valve implantation, that could have a different functional impact on elderly subjects, being less invasive.

Conclusions

In conclusion, our data show that aortic valve replacement in elderly subjects do not have negative effects on cognition and depression; on the contrary, the intervention leads in the medium-term to an improvement in neuropsychological scores. Also nutritional status seems to take advantage from AVR, as demonstrated by the improvement in MNA score in addition to the reduction in the percentage of people at risk for malnutrition at 6-month follow up.

Regarding physical performance, aortic valve replacement leads to a significant improvement in SPPB and in gait speed, which are considered indicators of good global health status. This functional improvement occurred without an increase in limbs muscle strength, as measured by handgrip and femoral quadriceps flexion and extension strength. Moreover, subjects who had a greater benefit from AVR were those with a worse performance at baseline.

Finally, all subjects in the middle-term perceived a better quality of life compared to baseline, in particular concerning physical role functioning, vitality, social role functioning and mental health.

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Table 1. General characteristics of subjects at baseline by gender.

	Women (n = 10)	Men (n = 12)	p-value *(Women vs Men)*
Age (ys)	76.4±2.7	76.7±4.5	n.s.
Height (m)	1.55±0.06	1.70±0.09	<0.0001
Body weight (Kg)	72.2±7.64	80.4±10.6	0.05
NYHA class I (%)	0	0	n.s.
NYHA class II (%)	77.7	75.0	n.s.
NYHA class III (%)	22.3	25.0	n.s.
NYHA class IV (%)	0	0	n.s.
Angina, %	22.2	16.6	n.s.
Sincope, %	11.1	0.0	n.s.
Echocardiographic parameters			
Aortic valve area (cm^2)	1.40±0.52	1.49±0.58	n.s.
Indexed aortic valve area (cm^2/m^2)	0.57±0.20	0.52±0.20	n.s.
Peak transaortic pressure gradient (mmHg)	83.11±27.55	73.96±15.40	n.s.
Mean transaortic pressure gradient (mmHg)	51.27±17.03	46.24±10.98	n.s.
Left ventricular ejection fraction (%)	62.2±8.0	59.0±9.4	n.s.
Multidimensional assessment			
Comorbidities			
CIRS-CI score	4.5±0.9	3.5±1.1	0.035
CIRS-SI score	1.9±0.2	1.7±0.1	0.050
Nutritional assessment			
BMI (Kg/m^2)	30.4±4.9	27.4±3.3	n.s.
Arm circumference (cm)	28.9±4.4	28.4±2.4	n.s.
Calf circumference (cm)	35.4±5.2	35.4±3.6	n.s.
Waist circumference (cm)	98.7±16.5	102.6±10.0	n.s.
MNA score	24.3±1.7	25.7±1.9	n.s.
Cognitive status and mood evaluation			
MMSE score	27.2±2.5	27.0±1.7	n.s.
MoCA score	21.5±4.4	24.9±2.3	0.041
GDS score	12.6±4.5	11.2±2.8	n.s.
Functional status			
ADL independent	5.6±0.5	5.9±0.3	n.s.
IADL independent %	95.8±6.2	98.3±5.7	n.s.
Physical performance			
SPPB [median (IQR)]			
Standing balance score	4 (4-4)	4 (3-4)	n.s.
4-meter gait speed score	3 (3-4)	4 (3-4)	0.05
Repeated chair stands score	4 (1-4)	4 (3-4)	n.s.
Total score	11 (8-12)	11 (9-12)	n.s.
Gait Speed (m/s)	1.02±0.82	0.82±0.21	n.s.
6-MWT (m)	301.3±124.4	442.9±71.7	0.004
Handgrip maximal strength (Kg)	21.3±7.2	42.8±9.8	<0.0001
Handgrip endurance (sec)	94.8±70.2	81.1±35.8	n.s.
Peak-torque extension (Nm)	50.4±5.8	91.0±28.2	<0.0001
Peak-torque flexion (Nm)	21.3±7.6	40.1±15.2	0.003
Isometric maximal strength (Nm)	78.2±16.4	140.1±42.9	<0.0001

NYHA: New York Heart Association; CIRS: Cumulative Illness Rating Scale (CI: Comorbidity Index; SI: Severity Index); BMI: Body Mass Index; MNA: Mini Nutritional Assessment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; GDS: Geriatric Depression Scale; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; SPPB: Short Physical Performance Battery; IQR: interquartile range; 6-MWT: six-minute walking test.

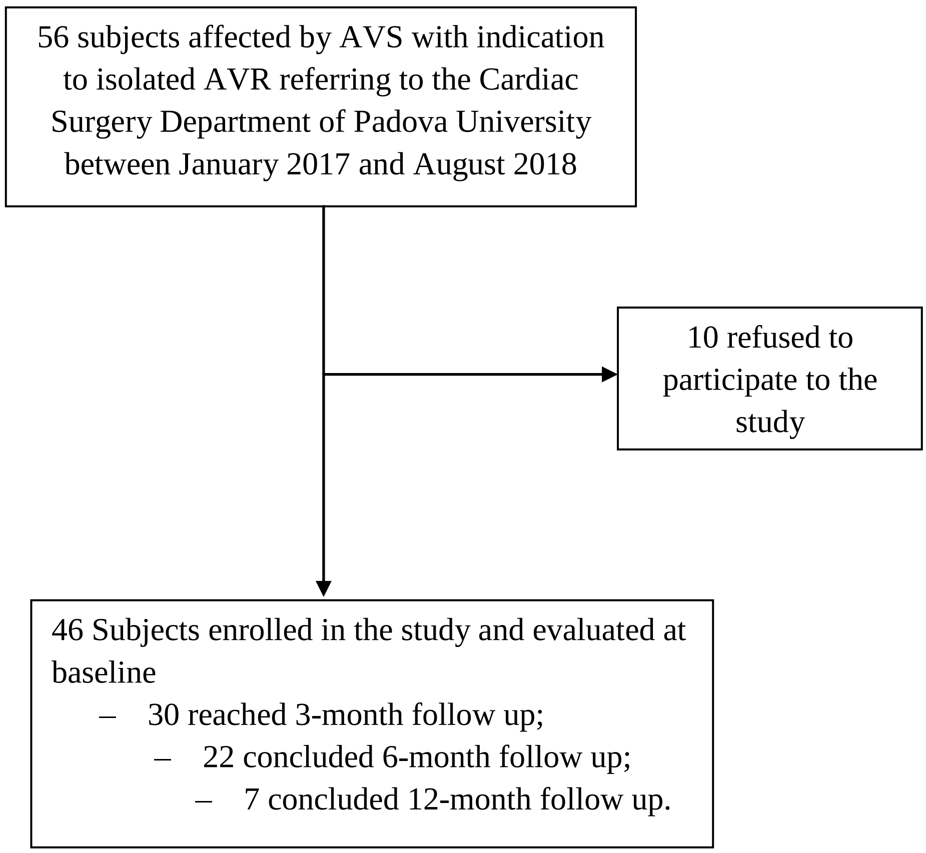
Table 2. General characteristics of the sample (n=22) at baseline and during follow up (FU).

	Baseline (T0)	45-days FU (T1)	3-month FU (T2)	6-month FU (T3)	p-value *(T0 vs T1)*	p-value *(T1 vs T2)*	p-value *(T2 vs T3)*	p-value *(T0 vs T2)*	p-value *(T0 vs T3)*
Indexed aortic valve area (cm^2/m^2)	0.51±0.10	0.83±0.15	1.35±0.20	1.32±0.18	0.03	0.01	n.s.	0.002	0.002
Peak transaortic pressure gradient (mmHg)	72.6±14.7	20.6±9.7	20.0±5.0	15.0±4.4	<0.0001	n.s.	n.s.	<0.0001	<0.0001
Mean transaortic pressure gradient (mmHg)	43.8±9.5	12.0±6.3	10.1±4.9	14.0±2.6	<0.0001	n.s.	n.s.	<0.0001	<0.001
Left ventricular ejection fraction (%)	58.0±9.7	54.1±6.7	55.4±6.1	58.7±6.5	n.s.	n.s.	n.s.	n.s.	n.s.
<u>*Multidimensional assessment*</u>									
Nutritional assessment									
Body weight (Kg)	76.6±10.3	73.9±10.8	75.4±11.9	76.7±11.5	0.001	0.001	0.015	n.s.	n.s.
BMI (Kg/m^2)	28.4±4.3	27.7±4.8	34.4±28.0	28.5±5.0	0.037	n.s.	0.016	n.s.	n.s.
Arm circumference (cm)	28.5±3.4	27.0±2.8	28.3±2.5	28.6±0.6	0.014	n.s.	n.s.	n.s.	n.s.
Calf circumference (cm)	35.1±4.3	34.3±4.7	35.8±3.6	35.8±0.5	n.s.	n.s.	n.s.	n.s.	n.s.
Waist circumference (cm)	100.3±13.4	98.1±11.4	100.3±11.2	101.1±2.7	n.s.	n.s.	n.s.	n.s.	n.s.
MNA score	25.0±1.8	23.4±2.5	25.4±2.1	26.6±0.2	0.028	0.003	0.030	n.s.	0.006
MNA score 23.5-17 (%)	28.6	52.6	28.6	0.0	0.015	0.018	0.002	n.s.	0.001
MNA score <17 (%)	0.0	0.0	0.0	0.0	n.s.	n.s.	n.s.	n.s.	n.s.
Cognitive status and mood evaluation									
MMSE score	26.6±2.2	26.6±2.2	27.3±1.9	27.9±1.6	n.s.	n.s.	0.050	n.s.	0.040
MMSE score <24/30 (%)	5.0	5.0	0.0	0.0	n.s.	n.s.	n.s.	n.s.	n.s.
MoCA score	22.9±4.2	24.1±3.4	24.1±2.9	25.0±2.4	n.s.	n.s.	n.s.	n.s.	0.016
MoCA score <26/30 (%)	80.0	71.4	73.3	76.2	n.s.	n.s.	n.s.	n.s.	n.s.
GDS score	12.4±3.4	11.3±3.8	11.7±4.6	10.7±4.4	n.s.	n.s.	n.s.	n.s.	n.s.
GDS score 11-16 (%)	50.0	53.5	40	23.9	n.s.	n.s.	n.s.	0.05	0.038
GDS score >16 (%)	10.0	14.2	13.4	14.3	n.s.	n.s.	n.s.	n.s.	n.s.
Functional status									
ADL independent	5.7±0.41	5.6±0.6	5.8±0.5	5.9±0.0	n.s.	n.s.	n.s.	n.s.	n.s.
IADL independent %	96.9±6.2	90.2±18.5	93.9±11.9	98.2±12.4	n.s.	n.s.	n.s.	n.s.	0.004
Physical performance									
SPPB [median (IQR)]									
Standing balance score	4 (4-4)	4 (3-4)	4 (3-4)	4 (4-4)	0.05	0.048	n.s.	n.s.	n.s.
4-meter gait speed score	4 (3-4)	4 (3-4)	4 (3-4)	4 (4-4)	n.s.	n.s.	n.s.	n.s.	0.05

	Baseline (T0)	45-days FU (T1)	3-month FU (T2)	6-month FU (T3)	p-value *(T0 vs T1)*	p-value *(T1 vs T2)*	p-value *(T2 vs T3)*	p-value *(T0 vs T2)*	p-value *(T0 vs T3)*
Repeated chair stands score	4 (2-4)	4 (3-4)	4 (3-4)	4 (3-4)	n.s.	n.s.	n.s.	0.05	0.05
Total score	11 (8-12)	12 (9-12)	11 (9-12)	12 (11-12)	n.s.	n.s.	0.038	n.s.	0.028
Subjects with SPPB total score ≤8 (%)	9.5	21.1	14.3	4.8	0.035	n.s.	n.s.	n.s.	0.025
Gait Speed (m/s)	0.94±0.23	0.90±0.20	0.91±0.20	1.10±0.09	n.s.	n.s.	n.s.	n.s.	0.05
6-MWT (m)	380.0±12.7	361.0±12.4	383.0±19.4	390.5±25.2	0.05	0.048	n.s.	n.s.	n.s.
Handgrip maximal strength (Kg)	33.7±14.4	29.9±11.1	31.7±13.9	33.5±3.0	0.008	n.s.	0.010	n.s.	n.s.
Handgrip endurance (sec)	88.8±55.4	78.0±38.4	81.6±41.2	75.9±7.8	n.s.	n.s.	n.s.	n.s.	n.s.
Peak-torque extension (Nm)	73.7±30.7	65.2±30.4	72.1±30.6	73.9±7.3	0.035	n.s.	n.s.	n.s.	n.s.
Peak-torque flexion (Nm)	32.1±15.1	26.3±9.9	31.1±16.3	34.1±5.1	0.05	n.s.	n.s.	n.s.	n.s.
Isometric maximal strength (Nm)	115.0±47.4	97.9±39.0	101.3±45.9	104.5±8.4	0.001	n.s.	n.s.	0.007	n.s.

BMI: Body Mass Index; MNA: Mini Nutritional Assessment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; GDS: Geriatric Depression Scale; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; SPPB: Short Physical Performance Battery; IQR: interquartile range; 6-MWT: six-minute walking test.

Figure 1. Flow chart illustrating patients selection process.



AVS: aortic valve stenosis; AVR: aortic valve replacement;

Figure 2. Prevalence of comorbidities in subjects at baseline by gender.

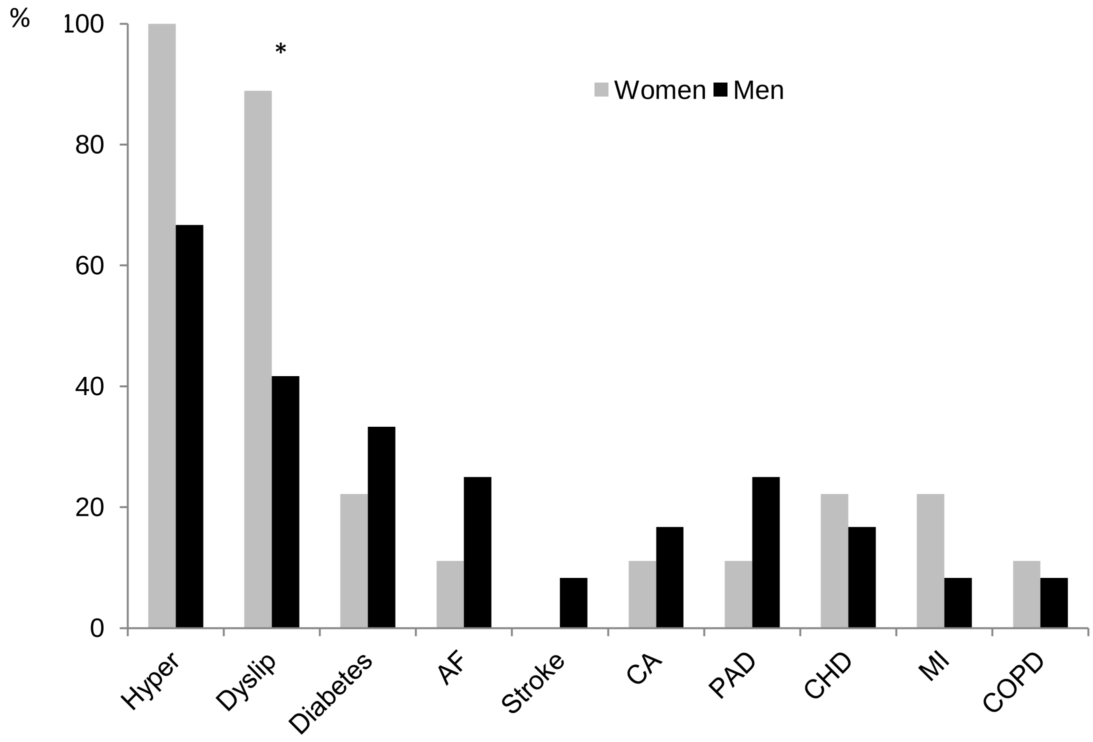


Figure legend

Hyper: hypertension; Dyslip: dyslipidemia; AF: atrial fibrillation; CA: carotid atherosclerosis; PAD: peripheral artery disease; CHD: coronary heart disease; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease.

* $p < 0.05$

Figure 3. SF36 scores at baseline in subjects divided by gender.

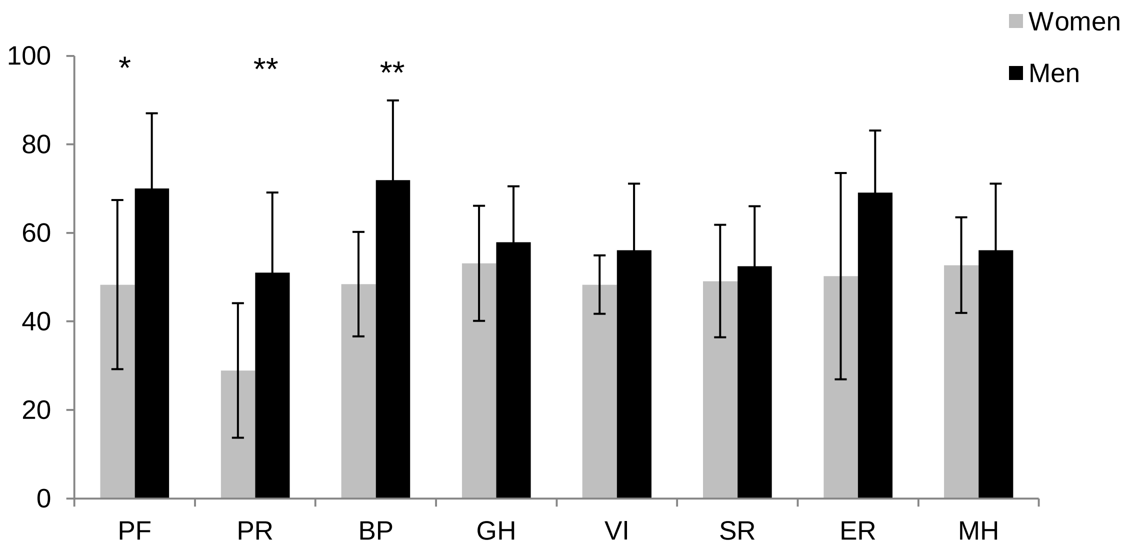


Figure legend

PF: physical functioning; PR: physical role functioning; BP: bodily pain; GH: general health perceptions; VI: vitality; SR: social role functioning; ER: emotional role functioning; MH: mental health.

* $p < 0.05$; ** $p < 0.01$

Figure 4. Mean score obtained by the studied population in SF36 items at baseline (T0) and during follow up.

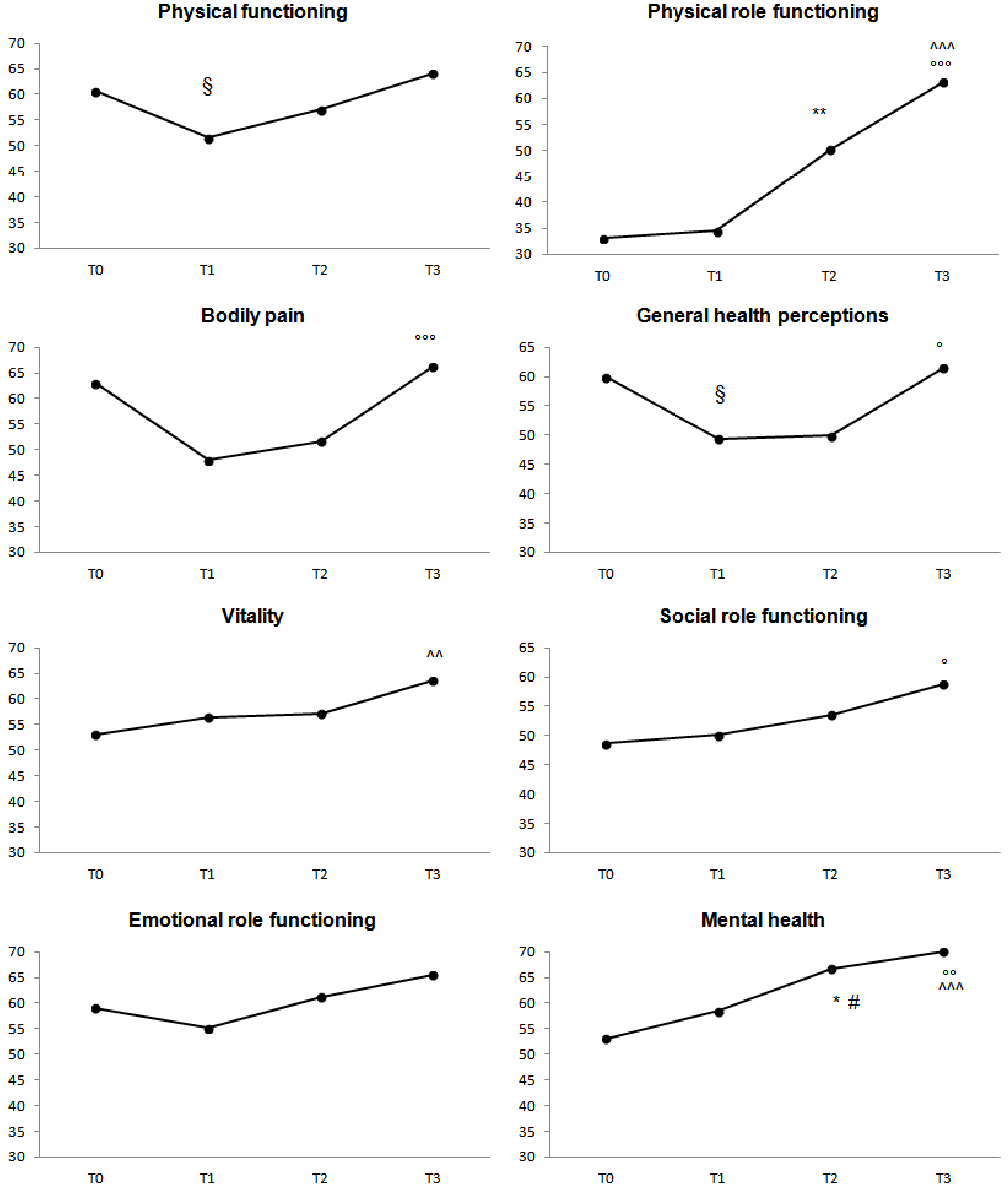


Figure legend

For T0 *vs* T1, §: p <0.05; for T1 *vs* T2, *: p <0.05, **: p <0.01; for T2 *vs* T3, °: p <0.05, °°: p <0.01, °°°: p <0.001; for T0 vs T2, #: p <0.05; for T0 vs T3, ^^: p <0.01, ^^^: p <0.0001.

Figure 5. Comparison between percentage of subjects with SF36 items score > 50 at baseline vs 6-month follow up.

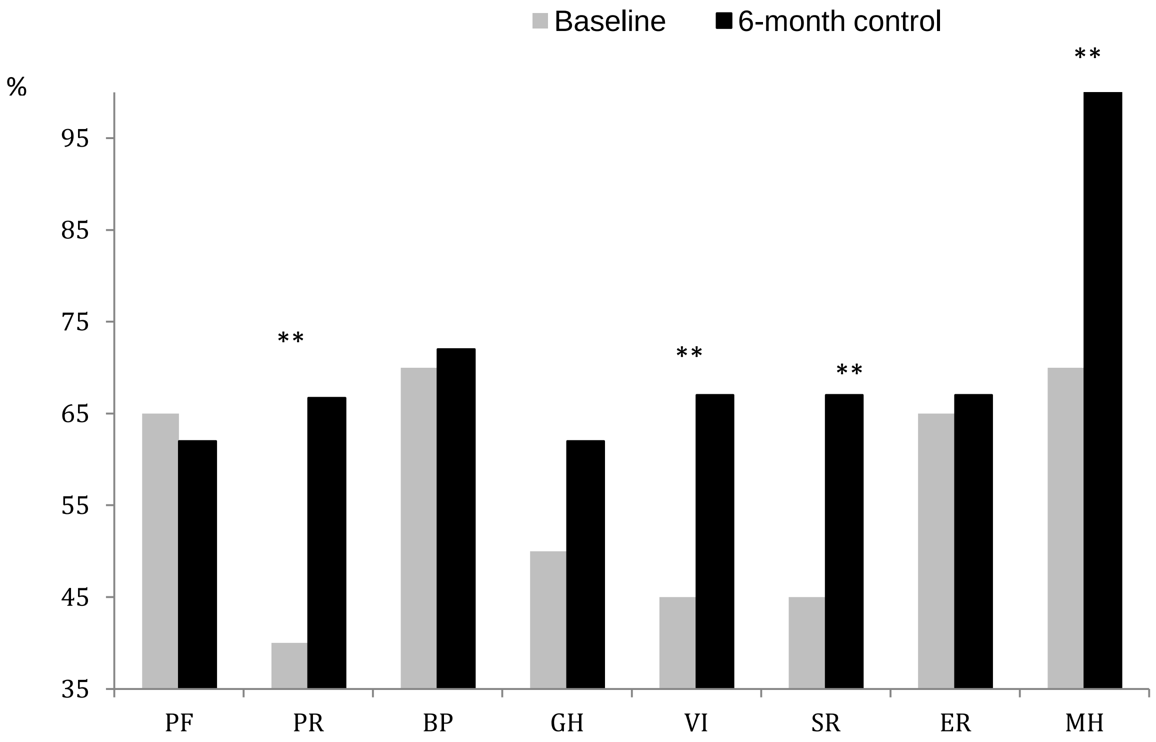


Figure legend

PF: physical functioning; PR: physical role functioning; BP: bodily pain; GH: general health perceptions; VI: vitality; SR: social role functioning; ER: emotional role functioning; MH: mental health.

** $p < 0.01$

Figure 6. Significant correlations between gate speed variations (6-month vs baseline) and baseline characteristics of subjects.

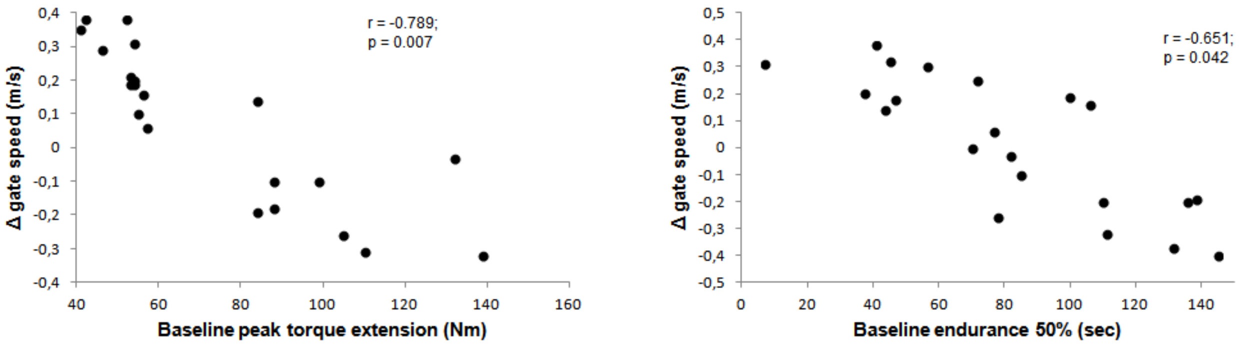
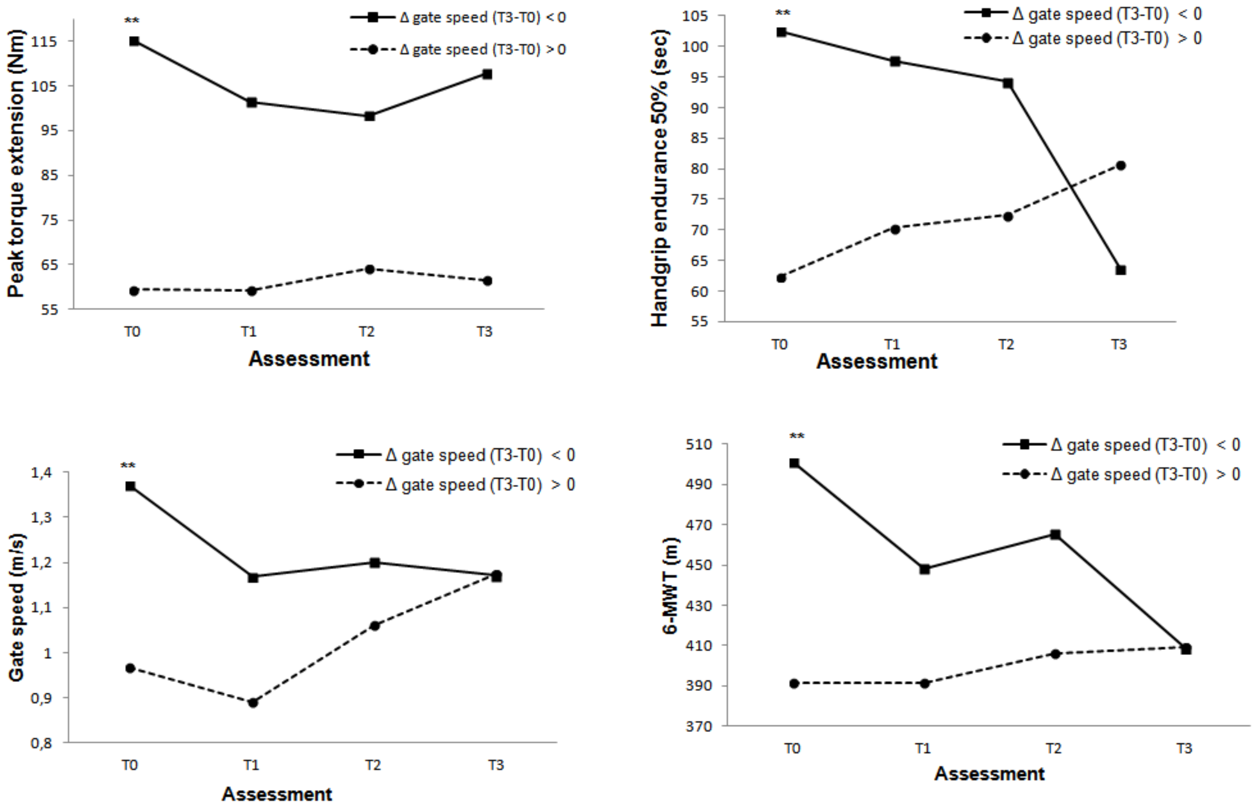


Figure 7. Mean peak torque extension, handgrip endurance, gait speed, SPPB score and 6-MWT distance in subjects divided by change in gate speed (6-month vs baseline) at each assessment visit.



** p < 0.01 for comparison between groups at the same time point