Total arterial compliance estimated by a novel method and all-cause mortality in the elderly: the PROTEGER study

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Abstract Aortic stiffness, assessed by carotid-to-femoral pulse wave velocity (PWV), often fails to predict cardiovascular (CV) risk and mortality in the very elderly. This may be due to the non-linear association between PWV and compliance or to blood pressure decrease in the frailest subjects. Total arterial compliance (C_T) is the most relevant arterial property regarding CV function, compared to local or regional arterial stiffness. A new method for C_T estimation, based on PWV, was recently proposed. We aimed to investigate the value of C_T to predict all-cause mortality at the elderly. PWV was estimated in 279 elderly subjects (85.5 ± 7.0 years) who were followed up for a mean period of 12.8 ± 6.3 months. C_T was estimated by the formula $C_T=k\times\mathrm{PWV}^{-2}$; coefficient k is body-size dependent based on previous in silico simulations. Herein, k was adjusted for body mass index (BMI) with a 10 % change in BMI corresponding to almost 11 % change in k. For a reference BMI$=26.2$ kg/m^2, $k=37$. Survivors ($n=185$) and non-survivors ($n=94$) had similar PWV (14.2 ± 3.6 versus 14.9 ± 3.8 m/s, respectively; $p=0.139$). In contrast, non-survivors had significantly lower C_T than survivors (0.198 ± 0.128 versus 0.221 ± 0.1 mL/mmHg; $p=0.018$). C_T was a significant predictor of mortality ($p=0.022$, odds ratio$=0.326$), while PWV was not ($p=0.202$), even after adjustment for gender, mean pressure and heart rate. Age was an independent determinant of C_T ($p=0.016$), but not of PWV. C_T, estimated by a novel method, can predict all-cause mortality in the elderly. C_T may be more sensitive arterial biomarker than PWV regarding CV risk assessment.

Keywords Arterial stiffness · Pulse wave velocity · Distensibility · Elasticity · Aorta · Cardiovascular risk

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Introduction

In our days, population ageing is an unprecedented phenomenon. In almost every country, especially the industrialized ones, the proportion of people over 60 years is growing faster than any other age group, as a result of both longer life expectancy and declining birth rates. Several parameters have been identified as

risk factors for mortality in frail elderly populations. Many great discoveries regarding arterial macro- and microcirculation from the antiquity (Karamanou and Androutsos 2010; Androutsos et al. 2012) as well as recent knowledge gained from prospective clinical studies have led to the appreciation that arterial ageing and impairment of physiological mechanical properties of arterial walls (i.e. stiffening) are indisputably predisposing factors for increased cardiovascular (CV) risk and mortality rates. However, in elderly and other populations, there is a controversy regarding the prognostic value of arterial stiffness as assessed by existing methodologies (Megnien et al. 1998; Meaume et al. 2001; Protogerou et al. 2007; Verwoert et al. 2012).

Compliance is a main biomechanical property of the arterial walls with established hemodynamic and pathophysiological relevance. *Arterial compliance* is the ability of the arterial wall to distend and increase volume with increasing transmural pressure. Arterial compliance as a property is the inverse of arterial stiffness. The classic definition of arterial compliance (C) is the change in arterial blood volume (ΔV) due to a given change in arterial blood pressure (ΔP); thus, $C = \Delta V / \Delta P$ (Spencer and Dennison 1963). When the left ventricle (LV) ejects into a compliant system, a slower rise in systolic pressure for a given stroke volume causes a lower wall stress and a lower oxygen consumption (McVeigh et al. 2007); namely, LV performance is maintained at lower energetic cost (Kolh et al. 2000). Furthermore, the stored blood volume during cardiac systole, by the distensible arterial walls, contributes to the maintenance of blood flow during cardiac diastole. On the other hand, a decrease in total arterial compliance (C_T) can cause an enhancement in pressure and flow wave amplitude and increase LV load (Kelly et al. 1992; Papaioannou et al. 2003; Mottram et al. 2005). Coronary perfusion may be also affected due the decline in diastolic pressure. In parallel, C_T reduction results to an increase in pressure wave speed, and consequently, the return of reflected waves at central aorta occurs during early systole, leading to an augmentation of peak systolic pressure and pulse pressure.

Several methods and techniques have been proposed for the non-invasive estimation of compliance of (1) a specific arterial location which is mainly assessed by ultrasound-based techniques (Stefanadis et al. 1990; Li and Khir 2011), (2) a whole arterial segment or region which is most commonly assessed by carotid-to-femoral pulse wave velocity (Van Bortel et al. 2012) and (3) the

entire arterial tree (Stergiopulos et al. 1995). In a theoretical and physiological basis, the most relevant arterial property, in respect to cardiac function and ventriculo-arterial coupling, is C_T rather than the stiffness of a single arterial location or segment, since C_T is a main parameter that influences aortic input impedance (Westerhof et al. 2010). Most methods of C_T estimation require both pressure and flow wave recording at the aorta (Stergiopulos et al. 1995, 1999; Segers et al. 1999). Consequently, these techniques are complex in their use with limited applicability in clinical research.

Thus, up to now, measurement of carotid-to-femoral pulse wave velocity (PWV) has prevailed in clinical practice as the most broadly applied method for the assessment of arterial stiffness. A great body of evidence and data indicates that aortic stiffness is an independent predictor of CV risk and mortality in several populations (Laurent et al. 2001; Blacher et al. 2002; Mattace-Raso et al. 2006; Mitchell et al. 2010). Nevertheless, other studies failed to prove the prognostic value of PWV in elderly populations or subjects with increased arterial stiffness (Megnien et al. 1998; Protogerou et al. 2007; Verwoert et al. 2012). The rationale behind the limited prognostic value of PWV in the aforementioned studies may be due to (1) the non-linear association between PWV and compliance as previously suggested (Vardoulis et al. 2012), (2) the non-linear association between PWV and age (Taviani et al. 2011) or (3) decrease of blood pressure (BP) in the frailest subjects and BP dependence of PWV.

Recently, a new method for C_T assessment was described (Vardoulis et al. 2012), based on the Bramwell-Hill theory (Bramwell and Hill 1922). This method allows the estimation of C_T only from aortic PWV with a correction based primarily on body size. The aim of the present study was to investigate the ability of C_T (estimated by this new method) to predict all-cause mortality in elderly people. Our hypothesis was that although, as previously published (Protogerou et al. 2007), aortic PWV fails to predict mortality in the elderly, C_T may have a predictive ability to detect individuals at increased risk.

Methods

Study cohort

A total of 331 consecutive patients examined at the geriatric departments of Charles Foix and Emile Roux

Hospitals, Ile de France from May 2000 to November 2001 were initially enrolled in the "PRonostic cardiovasculaire Optimisation Therapeutique En GERiatric Study" (PROTEGER study) (Protogerou et al. 2007; Zhang et al. 2010a, b). The inclusion criteria were as follows: age above 70 years old; history of CV disease including coronary heart disease, hypertension, cerebrovascular disease or any other CV events of the upper or lower limbs, abdominal or thoracic aorta or renal arteries; Mini Mental Status Examination greater than 15 of 30; absence of fatal disease with life expectancy up to 1 month; and willingness to give a written informed consent to participate in this study. Patients with cachexia (body mass index <17 kg/m^2) and/or evolutive cancer and/or advanced renal failure (plasma creatinine >250 μmol/L) were excluded from the study.

The study protocol was approved by the Committee for the Protection of Human Subjects in Biomedical Research of Saint Germain Hospital (Ile de France). Written informed consent was obtained from all participants. Further details regarding the study population and protocol have been described previously (Protogerou et al. 2007; Zhang et al. 2010a, b, 2012), and only parameters relevant to the present analysis are presented here.

Assessment of aortic stiffness and wave reflections

All measurements were performed in the morning with each subject being at the supine position after 15 min of rest. Brachial BP was measured by the semi-automatic oscillometric device Dynamap (Kontron). Aortic hemodynamics was also estimated by the use of generalized transfer function and applanation tonometry of the radial artery (SphygmoCor, AtCor, Sydney, Australia). Wave reflections were assessed by using augmentation index (AIx) which was calculated by pulse wave analysis as previously described (Vlachopoulos and O'Rourke 2000).

Aortic PWV was estimated using the Complior apparatus (Alam Medical, Paris, France). The distance covered by the pulse wave was measured directly from the carotid to the femoral artery, and the transit time was estimated by a previously described foot-to-foot method (Asmar et al. 1995). The superficial distance covered by the pulse wave was measured directly from the carotid to the femoral artery. It should be note that this method for distance assessment may overestimate PWV by approximately 2 m/s (Van Bortel 2006).

Estimation of total arterial compliance

The following mathematical equation relating C_T with aortic PWV was recently proposed, by using a theoretical approach based on the Bramwell-Hill theory (Bramwell and Hill 1922):

$$C_T = k \cdot \frac{1}{PWV^2}$$

where k is a coefficient that accounts for the contribution of local geometry and wave speed of each arterial segment and it was determined in silico (k=36.7 with 95 % confidence interval 36.2–37.2) (Vardoulis et al. 2012). Coefficient k was found to be primarily body-size-dependent. A good agreement regarding the proportionality of k values to the volume of the arterial tree was reported (Vardoulis et al. 2012); namely, an increase of arterial volume by 10 % (from a reference value of arterial volume) resulted in an 11.8 % increase in k value, while a 10 % volume reduction resulted in a 10.8 % decrease of k. Specifically, k values were 32.8, 36.9 and 41.2 for 10 % decrease, baseline and +10 % increase in arterial volume, respectively. For a reference arterial model that has been previously validated against human data (Reymond et al. 2009, 2011), baseline body mass index (BMI) was 26.23 kg/m^2. For each subject, an individualized k value was calculated based on the above-mentioned correspondence between percent changes in size and k coefficient.

Coefficient k is principally dependent on geometry and, specifically, on the weighted sum of all arterial segment volumes (Vardoulis et al. 2012). We have shown in silico that there is a good agreement regarding the proportionality of the k values to the volume of the arterial tree (Vardoulis et al. 2012). Hence, we can assume that coefficient k is principally dependent upon body size as estimated by BMI, but of course, this needs to be verified by further studies either in silico or with in vivo measurements.

Statistics

Distribution of continuous variables was assessed for normality by using the Kolmogorov-Smirnov test. Variables that were not normally distributed were transformed when needed (i.e. logarithmic transformation). The bivariate association between continuous variables was examined by the Pearson correlation coefficient. Multiple stepwise regression analysis was performed

to assess the independent determinants of AIx, PWV and C_T. Differences in arterial biomarkers between survivors and non-survivors were evaluated by Student's t test for independent samples. Cox regression analysis was performed to examine whether AIx, PWV and C_T predict all-cause mortality. Stepwise models were also constructed to assess confounding effects of other parameters. Receiver-operator (ROC) curves analysis was used to determine the predictive value of AIx, PWV and C_T. Paired comparisons of the areas under the ROC curves were also performed to examine whether C_T is superior than PWV and AIx in mortality prediction. Statistical significance was accepted for p values lower than 0.05. All comparison tests were two-sided. Statistical analysis was performed by SPSS (SPSS Inc., IL, USA) and Stata (StataCorp LP, TX, USA).

Results

Data from a total of 279 elderly subjects were finally analyzed (subjects with missing data of either PWV, BMI or mortality were excluded). All subjects were followed up for an average period of 12.8±6.3 months. A 33.7 % all-cause mortality was observed (94 subjects died during the 28 months of follow-up). Descriptive and hemodynamic characteristics of the study population are reported in Table 1.

Three widely used surrogates of arterial biomechanical properties were assessed: wave reflections (AIx), aortic stiffness (carotid-to-femoral PWV) and the newly proposed index of total arterial compliance (C_T). Parameters which are typically associated with the aforementioned biomarkers—such as age, gender, mean BP, heart rate and CV risk factors—were analyzed by linear regression analysis. AIx was significantly related to mean BP and heart rate, but not with age; PWV was correlated with mean BP and not with age; and finally, C_T was significantly related to age and gender but not with mean BP (Table 2).

In multivariate regression analysis, AIx was independently related to gender (AIx was higher in females than in males, $p=0.002$), mean BP ($p<0.001$) and heart rate ($p<0.001$). The stronger independent determinant of PWV was mean BP ($p=0.007$). Finally, C_T was independently related to age ($p=0.016$) and gender (females had higher total arterial compliance than males, $p=0.034$).

Table 1 Descriptive characteristics of the examined elderly population

Cardiovascular risk factors	
Age (years)	85.4±7.0
Gender (%, males)	25.8
Body mass index (kg/m^2)	26.9±5.3
Smoking (%)	21.2
Hypertension (%)	76
Diabetes (%)	20.1
Dyslipidemia (%)	17.3
Biochemical parameters	
Glucose (mmol/L)	5.8±2.2
Total cholesterol (mmol/L)	5.3±1.2
HDL (mmol/L)	1.1±0.3
LDL (mmol/L)	3.4±1.0
Triglycerides (mmol/L)	1.6±0.9
Hemodynamic and vascular parameters	
Systolic BP (mmHg)	132.5±19.5
Diastolic BP (mmHg)	65.8±12.1
Mean BP (mmHg)	91.3±15.4
Heart rate (b.p.m.)	71.3±12.5
Augmentation index (%)	27.8±13.5
PWV (m/s)	14.4±3.7

Data are mean ± standard deviation or percentages

BP blood pressure, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *PWV* carotid-to-femoral pulse wave velocity

AIx and PWV did not differ significantly between survivors and non-survivors (Table 3). On the contrary, non-survivors had significantly lower values of C_T compared to survivors ($p=0.018$, Table 3). BMI of survivors and non-survivors was 24.2±5.0 versus 23.3±4.7 kg/m^2, respectively ($p=0.167$).

The ability of AIx, PWV and C_T to predict all-cause mortality was first assessed by univariate Cox regression analysis. Among these three parameters, only C_T had a significant predictive value (odds ratio 0.326, $p=0.022$; Table 4).

Total arterial compliance predicted significantly all-cause mortality, in this elderly population, even after adjustment for the effect of gender, mean BP and heart rate (Table 5). The statistical significance was marginally lost ($p=0.078$) after adjustment for age. When all confounders (gender, mean BP, heart rate and age) were included in a single multivariate Cox regression model, the independent predictive value of C_T was observed at a significance level 0.097 (Table 5).

Table 2 Linear regression analysis: dependent variables were aortic pulse wave velocity (PWV), aortic augmentation index (AIx) and total arterial compliance (C_T) and independent variables were demographic and hemodynamic parameters as well as risk factors which are known to affect arterial biomechanical properties

	AIx (%)	PWV (m/s)	C_T (mL/mmHg)
Age (years)	−0.017 (0.788)	0.015 (0.795)	−0.116 (0.068) *
Gender (females)	0.098 (0.111) *	−0.104 (0.080)	0.095 (0.138) *
Mean BP (mmHg)	0.319 (<0.001) **	0.168 (0.005) **	−0.105 (0.099)
Heart rate (b.p.m.)	−0.311 (<0.001) **	0.060 (0.327)	−0.028 (0.665)
Smoking (yes)	−0.148 (0.244)	−0.010 (0.933)	−0.004 (0.974)
Diabetes (yes)	−0.137 (0.026)	0.096 (0.105)	−0.011 (0.869)
Dyslipidemia (yes)	0.034 (0.557)	−0.061 (0.304)	0.110 (0.084)

Values correspond to beta coefficients (p values)

$*p<0.05$; $**p<0.01$ (indicate the independent determinants of the dependent variable in a stepwise multiple regression model)

Receiver operator curve analysis (Fig. 1) showed that the area under the curve for C_T was 0.61, for PWV 0.569 and for AIx 0.483. The area under the curve of C_T was significantly higher than both PWV and AIx areas ($p=0.011$ and $p=0.032$, respectively).

Discussion

This is the first study demonstrating the significant value of total arterial compliance to predict all-cause mortality in an elderly population, when at the same time the typical measurement of carotid-to-femoral PWV and pressure wave reflections did not. A recently proposed method of C_T estimation (Vardoulis et al. 2012), using a modified approach of Bramwell-Hill theory, was applied on a previously investigated cohort of elderly people (Protogerou et al. 2007; Zhang et al. 2010a, b). It was revealed that C_T, assessed by this technique, is a significant predictor of all-cause mortality, independently from gender, mean blood pressure and heart rate.

Table 3 Comparison of aortic pulse wave velocity (PWV), aortic augmentation index (AIx) and total arterial compliance (C_T) between survivors and non-survivors

	Survivors	Non-survivors	p value
AIx (%)	142.9±24.3	143.2±20.4	0.912
PWV (m/s)	14.2±3.6	14.9±3.8	0.139
C_T (mL/mmHg)	0.221±0.1	0.198±0.128	0.018

Values are presented as mean ± standard deviation (number of valid cases)

Currently, the "gold standard" method for the assessment of arterial stiffness is measurement of the transmission velocity of a pressure wave between two arterial sites which is performed non-invasively, easily and reproducibly by the existing technologies. In contrast, traditional methods for C_T estimation are too complex since they require both blood pressure and velocity/flow recordings at the aorta. Most commonly, PWV is measured between carotid and femoral artery, providing a surrogate of aortic stiffness. Emerging evidence exists supporting that aortic PWV is an independent predictor of CV risk and mortality (Laurent et al. 2001; Blacher et al. 2002; Cruickshank et al. 2002). The inclusion of PWV in clinical practice, though, is still a conflicting issue. PWV measurement is proposed by the guidelines for the management of arterial hypertension of the European Society of Hypertension/European Society of Cardiology as a tool for assessment of subclinical target organ damage (Mancia et al. 2007). On the contrary, the guidelines for assessment of CV in asymptomatic adults, which were published in 2010 by the American College of Cardiology Foundation and the American Heart Association, raised several concerns

Table 4 Univariate Cox regression analysis of aortic pulse wave velocity (PWV), aortic augmentation index (AIx) and total arterial compliance (C_T), for the prediction of mortality at the elderly

	Odds ratio	95 % confidence intervals	p value
AIx (%)	0.998	0.990–1.007	0.686
PWV (m/s)	3.566	0.506–25.14	0.202
C_T (mL/mmHg)	0.326	0.125–0.853	0.022

Table 5 Multivariate Cox regression analysis of aortic pulse wave velocity (PWV), aortic augmentation index (AIx) and total arterial compliance (C_T), for the prediction of mortality at the elderly

| Model	Covariates	Dependent variable		
		AIx	PWV	C_T
Model-1	Gender	0.99 ($p=0.814$)	3.25 ($p=0.241$)	0.33 ($p=0.023$)
Model-2	Mean BP	0.99 ($p=0.767$)	3.75 ($p=0.19$)	0.32 ($p=0.019$)
Model-3	Heart rate	0.99 ($p=0.736$)	3.55 ($p=0.212$)	0.32 ($p=0.022$)
Model-4	Age	0.99 ($p=0.517$)	2.86 ($p=0.29$)	0.41 ($p=0.078$)
Model-5	Gender, mean BP Heart rate and age	1.00 ($p=0.952$)	2.13 ($p=0.472$)	0.43 ($p=0.097$)

Odds ratio (p value)

which restrict, at the moment, the recommendation of arterial stiffness measurement for clinical research (Greenland et al. 2010).

Although PWV can predict CV risk and mortality in various populations, it has limited predictive value in situations where arterial stiffness is increased, as previously discussed (Vardoulis et al. 2012). In an analysis which was performed within the framework of the Rotterdam Study, it was investigated whether aortic stiffness (assessed by PWV) improves the prediction of coronary heart disease; 2,849 elderly subjects with mean age of 71.5 years and mean PWV of 13.3 m/s were examined, and it was shown that there is a low additional value of aortic stiffness in the clinical management of coronary heart disease (Verwoert et al. 2012). In another clinical study by Megnien et al. (1998), aortic PWV and

distensibility did not predict coronary and extracoronary atherosclerosis in asymptomatic men at risk for CV disease. In the same direction, Matsusima et al. found that brachial-ankle PWV was not an independent predictor of coronary artery disease severity in a population of 205 patients (mean age 65 years) with increased PWV levels (16.4±3.6 m/s) who underwent coronary angiography (Matsushima et al. 2004). Another study on the prediction of mortality by PWV at the elderly showed that aortic PWV was an independent predictor of cardiovascular and not all-cause mortality in a population of 141 patients older than 70 years (Meaume et al. 2001). However, only PWV values higher than 17.7 m/s could predict CV mortality in that study (Meaume et al. 2001).

The aforementioned studies have revealed a limitation of PWV to predict CV risk and mortality in the

Fig. 1 Receiver-operator-curve analysis of aortic pulse wave velocity (PWV) and total arterial compliance (C_T) for the prediction of all-cause mortality. In order to compare directly the areas under the two curves, C_T was inversed so that high values of $1/C_T$, AIx and PWV have predictive value at the same direction
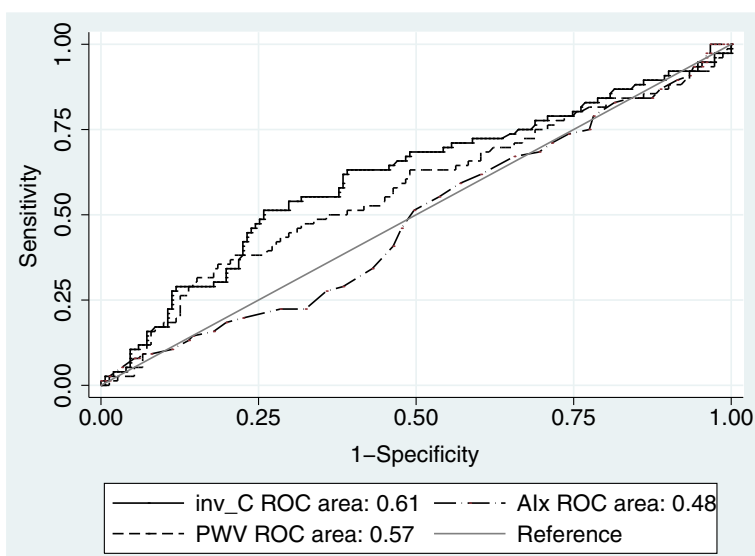
elderly or in subjects with increased arterial stiffness. A possible explanation for this may be due to the non-linear relationship between C_T and PWV. Another potential explanation is the fact that BP is decreased in the frailest subjects while at the same time PWV is BP dependent and thus PWV's predictive value may be confounded by BP levels.

In this study, C_T was found to predict all-cause mortality while PWV did not. The two aforementioned mechanisms can explain this finding. First, our approach for C_T estimation takes into consideration the non-linear relationship between compliance and PWV. Thus, small differences in PWV among subjects correspond to greater differences in C_T values (Fig. 2), rendering the latter parameter a more sensitive index. Secondly, although we verified the BP dependence of PWV in this population too, we also found that C_T was not related significantly with mean BP. Therefore, mean BP likely confounds the predictive value of PWV, but it does not affect that much the respective predictive value of C_T, in the examined elderly population. The latter finding was further supported by Cox regression analysis with both C_T and mean BP as independent covariates in a multivariate model for the prediction of all-cause mortality.

Another observation that might likely explain the superior prognostic value of C_T compared to PWV was that C_T better reflects the age-related effects on arterial properties; specifically, it was found that C_T is significantly related to age, while PWV is not.

From a pathophysiological point of view, there is no doubt that C_T is more relevant than regional or local arterial compliance (or their surrogate PWV), in terms of modulation of cardiac load, LV function, arterio-
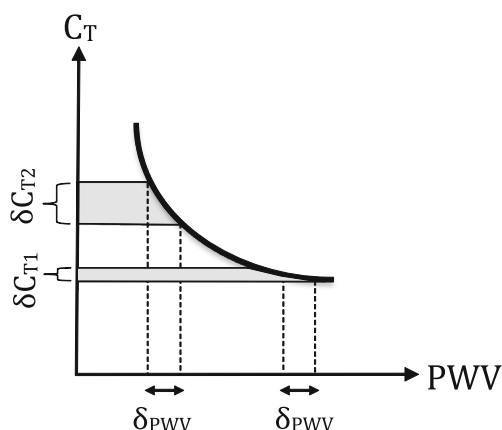
ventricular coupling and CV risk. The previously proposed method for C_T estimation (Vardoulis et al. 2012) can be widely and even retrospectively used, providing a more close approximation of global systemic arterial compliance. Of course, this method has strengths and weaknesses that should be acknowledged. Its advantages rely on the use of a broad, easy and simple method that is clinically available for the assessment of aortic stiffness (namely carotid-to-femoral PWV) combined with a simple adjustment for body size (i.e. BMI). The accuracy and precision of this method were found to be quite high in a previous validation study (Vardoulis et al. 2012). The fact that BMI does not always represent the arterial size, which is directly involved in the estimation of k coefficient, is considered as a weakness of this technique. Another limitation of the study is the small sample size which bounded the significance level of the predictive value of C_T (p value=0.097) when more covariates were entered in the multiple Cox regression model. It is estimated that a larger population (~350 subjects) would be enough to provide a p value lower than 0.05 for the independent prediction of all-cause mortality by C_T.

Finally, it should be mentioned that a previous relevant study of elderly women showed that systemic arterial compliance was not a significant predictor of cardiovascular events (Dart et al. 2006). The findings of the present study are not in line with those of that study which is mostly a result of major methodological differences between the two cohorts. In the study of Dart et al., only females were examined, while in this study, both genders were included. Furthermore, C_T was estimated by a much more complex technique (which was based on both aortic flow and pressure waves recording) than the simple one used in this study. Finally, Dart et al. examined the ability of C_T to predict "cardiovascular disease-free survival" and not total mortality per se. Since PWV was not measured in that study (Dart et al. 2006), direct comparison of the results of that cohort with the present one is not possible.

Fig. 2 Nonlinear relation between total arterial compliance (C_T) and pulse wave velocity (PWV)

Conclusions

Population ageing challenges health care systems to maximize the effectiveness of diagnostic and prognostic strategies in these subjects, aiming to the better understanding and management of their risk for CV complications and death. In this direction, a small step towards

a more accurate and timely assessment of CV risk and prediction of all-cause mortality in elderly populations may be achieved by the evaluation of total arterial compliance. This can be achieved by using a simple and non-invasive technique principally based on PWV and a modified Bramwell-Hill approach. The opinion of Sir William Osler (Canadian Physician, 1849–1919), one of the four founding professors of Johns Hopkins Hospital, best reflects the critical role of arterial properties on longevity: "Longevity is a vascular question, which has been well expressed in the axiom that man is only as old as his arteries". The age of the arterial tree is definitely reflected by its global compliance which remains a challenging property from methodological and clinical perspective.

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