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Figure 1. Kaplan-Meier mortality curves during the post-trial period between patients randomized to enalapril and to placebo. The data showed that the benefit in the enalapril group was apparent within the first year after trial close-out and persisted for the entire duration of the extended follow-up (Wilcoxon p = 0.01).

with 358 who had at least one adverse event. Considering the baseline characteristics, event-free patients were younger (54 vs. 61 years, p = 0.0001), had a lower functional class (New York Heart Association functional class I to II 97% vs. 87%, p = 0.003), and had a higher ejection fraction (32% vs. 29%, p = 0.002) at randomization. Event-free patients were also more likely to receive in-trial enalapril therapy than placebo (38 [62%] vs. 173 [48%], p = 0.04).

Our data indicated that early enalapril therapy reduced death and serious CV morbid events at 15 years in the Belgian SOLVD cohort. Specifically, at the end of this extended follow-up, a significant risk reduction in mortality was observed among patients treated early with enalapril compared with placebo, confirming our previous findings in the X-SOLVD trial. One mechanism that could explain these clinical benefits is the beneficial effect of enalapril on left ventricular remodeling and diastolic properties (5). Furthermore, prevention of early nonfatal cardiac ischemic events by enalapril during in-trial treatment (3) may lead to a late benefit in mortality. The original SOLVD data showed that enalapril reduced the incidence of cardiac ischemic events. The present study extended this finding by showing that the risk of death or nonfatal cardiac ischemic events remained significantly lower in the early enalapril group than in the delayed group. This suggests that earlier treatment initiation may confer long-term protection against atherosclerotic complications by a sustained beneficial effect on plaque stability and vascular remodeling (3,6). Moreover, our data suggested that on the event-free patients, middle-aged asymptomatic subjects derived the most protection from early enalapril therapy. This observation confirms the need to initiate enalapril without delay in patients with reduced ejection fractions, even in the absence of symptoms. However, we could not exclude that genetic variations might also explain this excellent long-term evolution.

In conclusion, in the 15-year follow-up of the Belgian SOLVD cohort, early enalapril therapy prevented late deaths and serious CV morbid events beyond the original trial period. Our data also refuted the suggestion that ACE inhibitors in patients with asymptomatic or minimally symptomatic ventricular dysfunction would not confer any long-term benefit except for masking the development of heart failure. Our study showed the importance of starting ACE inhibitor therapy as early as possible in patients with left ventricular systolic dysfunction to avoid any delay resulting in any significant loss of benefits years later.

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Short QT Interval and Atrial Fibrillation in Patients Without Structural Heart Disease

To the Editor: The short QT syndrome is a newly described clinical entity characterized by the presence of a short QT interval associated with cardiac tachyarrhythmias in otherwise healthy individuals. A genetic basis has been identified linking the disease to mutations in KCNH2 in the familial forms and a mutation in KCNQ1 in a sporadic form of the disease (1). The description of a novel, de novo gain of function mutation in KCNQ1, responsible for atrial fibrillation (AF) and short QT syndrome in utero, indicates that gain of function mutations in KCNQ1 channels can shorten the duration of both ventricular and atrial action potentials (2), which could account for the high incidence of AF in patients with short QT syndrome (3). Atrial fibrillation can occur in the

absence of detectable organic heart disease, so-called "lone AF," in about 30% of cases (4). Because the pathophysiology of lone AF remains poorly defined, we speculated that mechanisms underlying the high incidence of AF in short QT syndrome might also be responsible for the development of AF in the absence of structural heart disease. To test this hypothesis we examined QT interval duration in 165 consecutive healthy subjects presenting with an episode of AF (AF group). The control group included 165 age- and gender-matched subjects without any evidence of arrhythmia on a standard electrocardiogram (ECG).

Data on the AF group were collected at the hospital emergency department, and data on the control group were obtained in healthy individuals at the time of routine outpatient check-up as a part of national cardiovascular disease prevention program. Subjects treated with type I or type III antiarrhythmic drugs, antidepressive drugs, antihistamines, or macrolide antibiotics were not included in the study.

In all subjects, we recorded resting 12-lead ECGs at a paper speed of 25 mm/s on a Marquette Resting ECG recorder (Marquette Electronics Inc., Milwaukee, Wisconsin). With calipers on printed ECGs, the QT interval of each lead was measured from the beginning of the QRS complex to the visual return of the T-wave to the isoelectric line. When the T-wave was interrupted by the U-wave, the end of the T-wave was defined as the nadir between the T-wave and the U-wave. When the nadir was not clearly visible or the maximal T-wave amplitude did not exceed 0.25 mV, the ECG lead was excluded. All the QT interval measurements were performed with patients in sinus rhythm. Heart rate correction was done with the Bazett formula, and QTc interval duration was defined as the mean duration of all QTc intervals measured.

Differences between the AF and control groups were analyzed with 1-factor analysis of variance (ANOVA). Comparisons of categorical variables were made with a chi-square test. Both forward and backward stepwise linear regression analyses were used to identify predictive multivariate models. A p value < 0.05 was considered significant.

The two groups did not differ significantly with regard to age (62 ± 10 years in AF group vs. 61 ± 9 years in control group, $p = 0.67$), gender (male: 67% in AF group vs. 66% in control group, $p = 0.90$), history of hypertension (72% in AF group vs. 71% in control group, $p = 0.80$), or diabetes (10% in AF group vs. 8% in control group, $p = 0.76$). Similarly, we found no inter-group differences in left ventricular ejection fraction ($58.8 \pm 7.9\%$ in AF group vs. $61.1 \pm 10.3\%$ in control group, $p = 0.80$), dimensions of the left atrium (4.1 ± 1.2 cm in AF group vs. 4.0 ± 1.3 in control group, $p = 0.69$), resting heart rate (83 ± 23 beats/min in AF group vs. 78 ± 25 beats/min in control group, $p = 0.62$), or QRS complex duration (94 ± 15 ms in AF group vs. 91 ± 21 ms in control group, $p = 0.54$). No family history of premature sudden death was found in any of the groups; the history of syncope was present in 7% of patients from the AF group and in 4% of the control group ($p = 0.24$). The QTc interval of patients in the AF group, however, was significantly shorter compared with QTc interval in the control group (Fig. 1). Short QTc interval (<400 ms) was an independent predictor of AF occurrence in the multivariate analysis ($p = 0.002$), whereas hypertension, diabetes, decreased left ventricular ejection fraction (<60%), and increased left atrial size (>4 cm) were not.

Our findings demonstrate that even in the absence of genetically identifiable chanellopathies, patients with AF and no structural heart disease have significantly shorter QT intervals than their age- and gender-matched healthy counterparts. We therefore speculate that pathophysiological mechanisms that lead to shortening of QT interval (even of mild degree) might also play an important role in genesis of AF in structurally normal hearts. Action potential duration of ventricular myocardium is largely determined by the activation of delayed rectifier potassium current (IKs): with the loss-of-function mutation of IKs, the ventricular action potential is prolonged (clinically long QT syndrome); and in the gain-of-function mutation of IKs, it is shortened (clinically short QT syndrome) (5). The resulting enhancement of transmural dispersion of myocardial repolarization together with heterogeneous reduction in action potential duration creates a vulnerable window for ventricular arrhythmias. Similarly, the potassium current in human atrium shows kinetically distinguishable rapid and slow components, which might be of principal importance in determining atrial repolarization and its regulation by the autonomic nervous system and antiarrhythmic drugs (6). Therefore, the association of AF and short QT interval in our study might be partially explained by the alterations in IKs in both atrial and ventricular myocytes. Further studies are needed to better define the underlying pathophysiology and to investigate whether atrial and ventricular arrhythmias are generated by similar electrophysiological mechanisms.

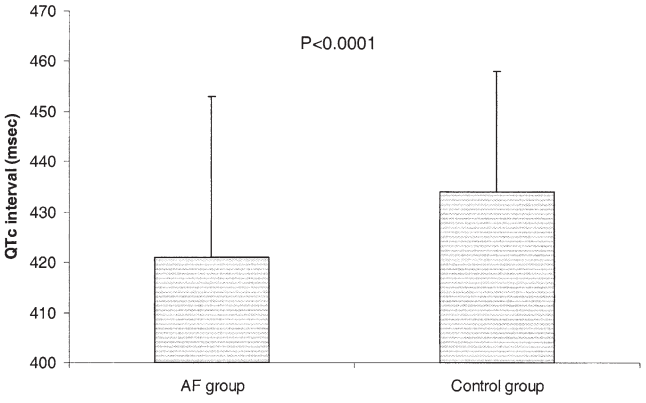

Figure 1. QTc interval duration in patients with atrial fibrillation and no structural heart disease (AF group) and in healthy subjects (control group).

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Association of Pulsus Paradoxus With Obesity in Normal Volunteers

To the Editor: First termed by Adolf Kussmaul in an 1873 manuscript (1), the physical finding of pulsus paradoxus (PP) has been described in numerous clinical situations, including constrictive pericarditis, cardiac tamponade, acute pulmonary hypertension, severe asthma, tension pneumothorax, and exacerbations of chronic obstructive pulmonary disease (2). Originally described as the disappearance of the palpated pulse during inspiration in the setting of pericardial constriction, PP has more recently been defined as a drop in systolic blood pressure (SBP) of >10 mm Hg with inspiration. This classic physical finding is discussed at all levels of medical training and is frequently used in clinical medicine.

Obesity, defined as a body mass index (BMI) >30 kg/m^2, is a condition affecting over 30% of the U.S. population and is a global epidemic (3). In obese patients, the compressive effects of increased abdominal girth on the chest wall and diaphragm might increase the work of breathing. We hypothesized that this exaggerated respiratory effort might lead to PP in otherwise healthy obese patients. Accordingly, we performed a prospective study to investigate the relationship between obesity and PP in patients undergoing elective cardiac catheterization.

Adult patients presenting for elective cardiac catheterization were prospectively studied for the presence of PP. These were patients with no known or suspected pericardial or pulmonary diseases by complete history and chart review. Inclusion criteria were: adult patients undergoing elective cardiac catheterization who consented to participate in the study. Exclusion criteria were: 1) any known cause of PP, to include history of chronic obstructive pulmonary disease, active or chronic pericardial diseases, active asthma exacerbation, or use of any bronchodilating medications; 2) urgent need for catheterization (e.g., ST-segment elevation myocardial infarction or hemodynamic instability); 3) right ventricular infarction; 4) recent pulmonary embolism; 5) pregnancy; or 6) decompensated heart failure.

On the day of cardiac catheterization, a physical examination was performed to exclude the presence of pulmonary or pericardial disease. Height, weight, and body circumferences at the umbilical and xiphoid levels were measured. A limited two-dimensional transthoracic echocardiogram was performed to exclude occult pericardial effusion and to assess for structural changes consistent with constrictive pericardial disease. No patient was noted to have occult pericardial effusion or significant structural enlargement of the heart chambers. Pulsus paradoxus was first measured noninvasively with sphygmomanometry and then invasively assessed within 1 h at the time of cardiac catheterization. By convention, a PP value of >10 mm Hg was considered abnormal.

Table 1. Demographic Characteristics of the 101 Study Participants

	Non-Obese (n = 64)	Obese (n = 37)	p Value
Age (yrs)	58 ± 12	57 ± 13	0.69
Gender, male (%)	52 (81.3%)	26 (70.3%)	0.23
Smoking history, n (%)			
Active	14 (23%)	9 (25%)	0.68
Prior	24 (39.3%)	11 (30.6%)	
None	23 (37.7%)	16 (44.4%)	
Coronary disease, n (%)			
None	26 (40.6%)	20 (54%)	0.107
1-vessel	8 (12.5%)	8 (21.6%)	
2-vessel	16 (25%)	3 (8.1%)	
3-vessel	14 (21.9%)	6 (16.2%)	
Blood pressure (mm Hg)			
Systolic	144.6 ± 23.3	142.9 ± 20.5	0.72
Diastolic	77.5 ± 10.5	78.4 ± 9.6	0.65
Mean	104.2 ± 12.9	104.5 ± 11.7	0.91
Left ventricular end-diastolic pressure (mm Hg), n = 59	18.1 ± 4.4 (n = 35)	20.2 ± 5.1 (n = 24)	0.10
Pulse pressure (mm Hg)	67.1 ± 23.1	64.5 ± 18.9	0.56
Height (cm)	175.2 ± 4.1	173.9 ± 5.6	0.54
Weight (kg)	81.8 ± 5.7	105.0 ± 8.0	<0.001
BMI (kg/m^2)	26.6 ± 1.4	34.7 ± 2.2	<0.001
Girth, umbilical (cm)	103.6 ± 4.8	122.2 ± 6.1	<0.001
Girth, xiphoid (cm)	101.8 ± 8.9	113.5 ± 9.4	<0.001

Values displayed as mean ± standard deviation.
BMI = body mass index.