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ORIGINAL COMMUNICATION

Heart failure in acute ischemic stroke

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Abstract *Background* To determine the impact of heart failure (HF), with preserved or decreased left ventricular function (LVF), on outcome in patients with acute ischemic stroke (AIS). *Methods* We studied 503 unselected ischemic stroke patients. Poor outcome was defined as moderate-severe disability or death at 90 days. We analyzed the association between poor outcome and HF with preserved LVF or decreased LVF (systolic HF: ejection fraction lower than 50 %). We tested this association adjusted by possible confounders in a logistic regression model. *Results* 89 patients (17.7 %) had HF; 49 patients (9.7 %) with systolic HF, and 40 (8 %) patients with HF and preserved LVF. HF with preserved LVF patients were older [79.4 (7.9) vs. 74.3 (10.4), p = 0.013], more likely to be women [p < 0.001, OR = 8.61, 95 % CI (3.3–22.6)], and with lower current smoking habits [p = 0.018, OR = 8.77 (1.1–72.6)] than patients with systolic HF. 151 patients (30 %) had poor outcome. We found an independent association with initial stroke severity, systolic HF (adjusted OR = 3.01), HF with preserved LVF (adjusted OR = 2.52), thrombolytic treatment, statin pre-treatment (as protectors) and poor outcome. *Conclusion* Both forms of HF (with or without decreased systolic function) are associated with poor outcome in AIS.

Key words cerebrovascular diseases · heart failure

Introduction

Several heart disorders such as atrial fibrillation, ischemic heart disease, heart failure (HF), and decreased left ventricular function (LVF) have been associated with a high severity, increased mortality, and poor outcome in patients with stroke [3, 4, 7, 10, 20, 23]. HF is a clinical syndrome characterized by increased tissue/organ fluids and decreased tissue/organ perfusion. Due to the population's aging, the frequency of HF has increased, thus contributing to the rise in mortality rates observed in recent years [18, 22, 27]. HF usually appears in patients with decreased left ventricular ejection fraction (EF), constituting systolic heart failure (SHF). However, patients with decreased left ventricular function do not always have symptoms of HF and clinical HF might be present in patients with preserved left ventricular function. This second condition is called HF with preserved systolic function [18, 27, 28]. The repercussion of both forms of HF on outcome of stroke patients has not been previously studied. The aim of our study was to an-

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alyze the impact of SHF and HF with preserved LVF on outcome after acute ischemic stroke (AIS).

Patients and methods

A total of 540 consecutive patients with a diagnosis of AIS according to the World Health Organization criteria [2], and with functional independence previous to stroke onset were admitted to the Neurology Department of the Hospital del Mar, Barcelona, from September 2004 to October 2006. 37 patients were excluded from analysis due to an incomplete/inadequate cardiac study or lost follow-up. The remaining 503 patients constituted the definitive study cohort. Time from stroke onset to hospital admission was registered in all patients. When the onset of the neurological symptoms was unknown, or occurred while sleeping, the stroke onset was established as the last time that the patient was seen free of symptoms. The severity of the stroke was assessed at hospital admission by a trained neurologist using the National Institutes of Health Stroke Scale (NIHSS) [5] and disability by punctuation in the modified Rankin Scale (mRS) [25]. Vascular risk factors were obtained from patients, relatives, and/or prior medical records. We used the following definitions: arterial hypertension (evidence of at least two blood pressure measurements, systolic > 140 or diastolic > 90 mm Hg recorded on different days before or one week after stroke onset, or previous medication use); diabetes (fasting glucose ≥ 5.6 mmol/L or use of diabetes medication); hyperlipidemia (serum cholesterol concentration > 5.6 mmol/L or serum triglyceride concentration > 1.7 mmol/L, or medication use); peripheral arterial disease (documented prior history of intermittent claudication or a resting ankle-brachial index < 0.90 in any leg); ischemic heart disease (documented history of myocardial infarction and/or angina pectoris); chronic or paroxysmal atrial fibrillation; current smoking habits; prior use of antithrombotic drugs (antiaggregant or anticoagulant) or statin treatment before stroke onset; and prior history of stroke. Endovenous thrombolytic treatment with rt-pa was administered based on the European Medicines Evaluation Agency Criteria (SITS-MOST criteria) in the first three hours after stroke onset. The arterial study included at least two of following explorations in all patients: a continuous extracranial or pulsate intracranial Doppler study, carotid duplex, MRI-angiography, CT-angiography and/or arteriography performed during hospitalization and interpreted by a trained neurologist or radiologist. Large artery atherosclerotic disease was defined by the detection of intra- or extracranial arterial stenosis ≥ 50 %. Data at 90 days after stoke onset were obtained from direct patient examination or by phone call (n = 42). The end-point of study was poor outcome defined as moderate-severe disability, or death (mRS 3 to 6) at 90 days.

Cardiac study

Diagnosis of HF was established by a trained cardiologist (with previous well-documented history or performed during hospitalization) based on standard clinical criteria from the Framingham Study [19]. SHF was defined as those patients with symptoms and signs of HF and a decreased LVF (ejection fraction < 50 %) [9]. As previously established, the measurement of diastolic function is not necessary for the diagnosis of HF with preserved LVF (ejection fraction ≥ 50 %) [29]. The cardiac study consisted of an echocardiogram to obtain parasternal views with optimal orientation to maximize left ventricular (LV) internal diameters. Echocardiograms (parasternal and apical views) were obtained with the patient resting supine in the left lateral position. The overall 1-dimensional LV measurements and the 2-dimensional views were obtained according to the recommendations of the American Society of Echocardiography. This method has been shown to permit a reliable estimation of LV systolic function [15–21]. Echocardiographic explorations were performed at hospital admission or during the 3 months following stroke onset (mean days 8.40 ± 3.97: range 2–34) and interpreted by a trained cardiologist. We included 47 patients in whom the echocardiographic study was performed during the 6 months before stroke and without new symptomatic cardiac episodes during this period.

Statistical analysis

For the univariate analysis we used the T-test for continuous variables or U of Mann-Whitney when normality distribution was difficult to assume. Chi^2 test was used for differences in proportions. Variables analyzed in the univariate model were age, initial stroke severity, male gender, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, antithrombotic and statins pre-treatments, lacunar stroke, carotid atherosclerosis ≥ 50 %, previous diagnosis of ischemic heart disease, arterial peripheral disease, and stroke. The multiple logistic regression analysis was performed by forward stepwise method introducing SHF, HF with preserved LVF, and the previous described factors. Initial stroke severity was categorized following the usual criteria: NIHSS score < 7 (n = 185), NIHSS 7–14 (n = 80), and NIHSS score > 14 (n = 192). Age was categorized into 4 groups using quartiles (< 63, 64 to 73, 74 to 78, and > 78 years). Thereafter, the remaining variables were cross-tabulated to discard multicollinearity. We did not include the time to hospital admission in the multivariable model due to its interaction with initial severity, and because there was no repercussion on the objective of the study. Finally, we repeated the test introducing non-categorized continuous variables (age, initial stroke severity) and separately analyzed 90-day mortality and 90-day poor outcome in order to detect possible statistical bias. It was concluded in all cases that each model fit was adequate.

Ethics

Study data were collected from our clinical protocols which fulfilled the local ethical guidelines. All patients signed an informed consent accepting the data storage.

Results

Of the 503 patients studied, 278 were men (55.3 %). Mean age was 70.6 (SD: 12.1) years (range 34–98). Median initial stroke severity measured by the NIHSS was 5 (q1–q3: 3–10), mean 7.02 (6.1) (range 0–28). Patients excluded due to incomplete data or follow-up had no differences in initial stroke severity, poor outcome at hospital discharge (19/37), vascular risk factors, or clinical HF (4/37). They did, however, have a higher age (mean 78.28 ± 8.20); $p < 0.001$.

Cardiac data and initial stroke severity

A total of 89 patients (17.7 %) had HF; 49 (9.7 %) had SHF, and 40 (8 %) had HF with preserved LVF. Baseline clinical data are summarized in Table 1. HF patients had higher initial stroke severity, higher prevalence of atrial fibrillation and ischemic heart disease, higher percentage of pretreatments, older age, and lower current smoking habits and lacunar stroke compared to patients without HF. No differences in time to hospital admission

Table 1 Baseline characteristics of stroke patients related to presence of heart failure

	Heart failure		
	Yes %	No %	p
Initial severity	9.81 ± 7.6	6.42 ± 5.5	**p < 0.001**
Age	76.63 ± 9.67	69.38 ± 12.2	**p < 0.001**
Gender (male)	49.4	56.5	p = 0.223
Hypertension	76.4	67.9	p = 0.113
Diabetes mellitus	36	33.1	p = 0.604
Hyperlipidemia	43.8	51.7	p = 0.178
Current smoking	11.2	27.8	**p = 0.001**
Ischemic heart disease	43.8	16.7	**p < 0.001**
Previous stroke	20.2	16.7	p = 0.421
Peripheral arterial disease	22.5	10.4	**p = 0.002**
Atrial fibrillation	57.3	22.2	**p < 0.001**
Antithrombotic pre-treatment	29.2	17.9	**p = 0.015**
Pre-treatment with statins	27	18.8	p = 0.084
Lacunar stroke	13.5	29	**p = 0.003**
Large arterial atherosclerosis	16.9	21.3	p = 0.350
Thrombolytic treatment	10.1	5.3	p = 0.088

were detected by the presence of HF [10.66 vs. 11.15, p = 0.817]. HF with preserved LVF patients were older [79.4 (7.9) vs. 74.3 (10.4), p = 0.013], more frequently women (71.4 % vs. 22.5 %), p < 0.001; OR = 8.61, 95 % CI (3.3–22.6), and with lower current smoking habits (2.5 vs. 18.4), p = 0.018; OR = 8.77 (1.1–72.6) than patients with SHF. No differences in the initial stroke severity [median NIHSS 6 (q1-q3: 4–13) vs. 7 (q1–q3: 4.5–16), p = 0.250] were registered. Patients with HF had a past history of ischemic heart disease (prior myocardial infarction or significant coronary pathology) in 39 cases (7 patients with bypass and 15 with angioplasty plus stent), hypertensive heart disease in 27, valvular heart disease in 9, and other causes or unknown causes in 14 cases.

Factors related to stroke outcome

After 90 days from stroke onset, 151 patients (30 %) had poor outcome (mRS from 3 to 6). The 90-day mortality rate was 10.3 % (52 cases). Factors associated with poor outcome are shown in Tables 2 and 3. We found an independent association between SHF (adjusted OR = 3.01), HF with preserved LVF (adjusted OR = 2.52), initial stroke severity, thrombolytic treatment, and statin pre-treatment with poor outcome. Patients with poor outcome arrived earlier at the hospital [8.99 vs. 11.99, p < 0.001]; this is probably related to the higher clinical severity [patients with initial severity ≥ 7: 6.75 hours vs. 13.57, p < 0.001].

Table 2 Factors related with poor outcome

	Poor Outcome		
	Yes n (%)	No n (%)	p
Gender (male)	72 (47.7)	206 (58.5)	**p = 0.025**
Initial severity	11.75 ± 7.27	4.99 ± 4.11	**p < 0.001**
Age	73.91 ± 11.1	69.27 ± 12.2	**p < 0.001**
Hypertension	111 (73.5)	238 (67.6)	p = 0.188
Diabetes mellitus	54 (35.8)	115 (32.7)	p = 0.501
Hyperlipidemia	68 (45)	185 (52.6)	p = 0.122
Current smoking	30 (19.9)	95 (27)	**p = 0.090**
Ischemic heart disease	35 (23.2)	69 (19.6)	p = 0.364
Previous stroke	26 (17.2)	61 (17.3)	p = 0.973
Peripheral arterial disease	23 (15.2)	40 (11.4)	p = 0.230
Atrial fibrillation	63 (41.7)	80 (22.7)	**p < 0.001**
Systolic heart failure (HF)	29 (19.2)	20 (5.7)	**p < 0.001**
HF with preserved function	20 (13.2)	20 (5.7)	**p = 0.004**
Antithrombotic pre-treatment	57 (37.7)	98 (27.8)	**p = 0.027**
Pre-treatment with statins	23 (15.2)	79 (22.4)	**p = 0.065**
Lacunar stroke	19 (12.6)	113 (32.1)	**p < 0.001**
Large arterial atherosclerosis	32 (21.2)	71 (20.2)	p = 0.795
Thrombolytic treatment	15 (9.9)	16 (4.5)	**p = 0.023**

Table 3 Factors independently associated with poor outcome. Adjusted OR obtained by logistic regression model

	Adjusted OR (95 % CI)	p
Initial severity	3.928 (2.837–5.438)	p < 0.001
Systolic heart failure (HF)	3.012 (1.330–6.822)	p = 0.008
HF with preserved function	2.523 (1.127–5.649)	p < 0.001
Pre-treatment with statins	0.316 (0.149–0.673)	p = 0.003
Thrombolytic treatment	0.468 (0.253–0.865)	p = 0.015

Discussion

Cardiac disorders can etiologically justify up to 20 % of all strokes with serious therapeutic implications [1, 11]. In this respect, recent studies have shown that HF and mild left ventricular dysfunction are associated with an increased risk of ischemic stroke [3, 11]. Moreover, HF has been related with poor outcome after stroke [3, 10, 20] although the direct implication of HF with preserved LVF has not been previously studied. We analyzed the individual influence of HF with preserved LVF in stroke prognosis after adjusting for possible confounders such as vascular risk factors and pre-treatments. We found that stroke patients with HF with preserved LVF were older, with lower current smoking habits, and more frequently women than SHF patients, as seen in recent reports [6]. Nevertheless, there were no differences in initial neurological severity between HF with preserved LVF and SHF patients. We observed an independent association between both factors and poor outcome with similar adjusted Odds ratio. The two HF

conditions have not been previously analyzed individually with respect to their deleterious effect in stroke outcome. It is possible that other mechanisms are involved in the physiopathology of HF in addition to a decreased systolic function that may be harmful for stroke patients. An apparently obvious explanation for the independent relationship between HF and poor outcome in stroke patients may be related to its underlying causes: atherosclerotic coronary disease, hypertensive disease, and valvular disease. These factors are associated with a higher atherosclerotic burden [26], endothelial dysfunction [13], more complex treatments, and a higher risk of death [22] or systemic-embolic complications [9]. However, these considerations are present in both conditions of HF. HF with preserved LVF patients have a different myocardial structure and function [12, 28], similar reduced exercise capacity and neuroendocrine activation, and possibly a lower influence in the cerebrovascular reactivity than SHF patients [8, 14, 16, 17, 24]. The increased risk of death and decreased exercise capacity, which might interfere with the rehabilitation process after stroke, could have an influence on prognosis HF with preserved LVF patients. It is, however, difficult to explain how the different myocardial structure and function, or the endocrine activation, may have a directly negative influence. We hypothesize that other unknown mechanisms of HF with preserved LVF could have a harmful influence in stroke patients.

There are some limitations of our study. We have not measured diastolic function; therefore, the association between diastolic function and poor outcome can not be validated. HF with preserved LVF patients could have normal diastolic function, and patients with diastolic dysfunction do not always have symptoms of HF. Moreover, in some cases we have used echocardiographic data obtained before stroke onset (n = 47) although in none of the cases did the patients experience new cardiac episodes.

In summary, there is a strong relationship between cardiac data and stroke outcome. This relationship is independent of initial stroke severity, demographic data or vascular risk factors, and is also detected in patients with preserved LVF. Greater knowledge of cardiac function could help us to take clinical and therapeutic decisions in order to improve the outcome of stroke patients. New studies analyzing other echocardiographic parameters, as well as the impact of diastolic function on acute stroke, are necessary to better understand the relationship between cardiac dysfunctions and stroke outcome.

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