Yield of Echocardiography in the Evaluation of Cerebral Ischemic Events: A Single Center Cohort Study

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Background: Echocardiography (ECO) is frequently used as a screening test in patients with acute ischemic brain disease. We aimed to evaluate the additional information and therapeutic impact resulting from ECO in these patients. *Methods:* We conducted a prospective study performing ECO on consecutive patients with ischemic stroke or transient ischemic attacks, admitted to our centre between February 2013 and May 2017. *Results:* A total of 696 patients were included (female, 57.3%; mean age, 70 ± 15.3 years). Seven hundred thirty two echocardiographic examinations were performed (696 transthoracic and 36 transesophageal). Echocardiography yielded findings judged of clinical importance in 142 patients (20.4%, 95% CI 17.5-23.5). The most frequent of these were left atrial volume enlargement or a normal evaluation. Echocardiography findings resulted in changes in the management of 76 patients (10.7% 95% CI 8.8-13.4); initiation of anticoagulation therapy, administration of IV antibiotic therapy, cardiac surgeries, or other pharmacological therapies occurring in 42 cases (6%). The presence of coronary heart disease (OR: 2.64 95% CI 1.34-5.25), atrial fibrillation (OR: 0.24;

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Received May 15, 2018; revision received October 11, 2018; accepted October 29, 2018.

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[2]Rodrigo Ibañez-Arenas reports no conflicts of interest.

[3]Martin Larico reports receiving a research grant from Clínica Alemana de Santiago. Personal fees from Boehringer Ingelheim for participation in Anticoagulation Academy − ESTAR. Personal fees from Thrombosis Research Institute as GARFIELD Registry co-investigator.

[4]Eloy Mansilla reports no conflicts of interest.

[5]Juan Almeida reports no conflicts of interest.

[6]Verónica Olavarría reports receiving a research grant from Clínica Alemana de Santiago.

[7]Paula Muñoz-Venturelli reports receiving a research grant from Clínica Alemana de Santiago.

[8]Alexis Rojo reports no conflicts of interest.

[9]Gabriel Cavada reports no conflicts of interest.

[10]Pablo M. Lavados reports research grants from The George Institute and Clínica Alemana de Santiago during the conduct of the study; personal fees from Bristol Meyer Squibb for atrial fibrillation and stroke advisory board; an unrestricted research grant from Lundbeck; personal fees from AstraZeneca and Bayer as SOCRATES and ESUS NAVIGATE trials national leader and a Chilean Government research grant for the ÑANDU project outside the submitted work.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.10.042

95% CI, 0.2-0.69), and admission NIHSS (OR: 1.04; 95% CI, 1.01-1.09), were the variables associated with changes in management. *Conclusions:* In unselected patients with acute ischemic stroke ECO had a low yield of additional information, and it changed management in a small percentage of patients.
Key Words: Acute stroke—ischemic stroke—echocardiography—diagnosis

Introduction

Stroke is a frequent cause of deaths in many countries,[1] 85 % of them of ischemic origin with cardiac embolism explaining almost 40% in some hospital series.[2] Half of these cardioembolic events are associated with atrial fibrillation (AF),[3] that can be detected by electrocardiogram (ECG), telemetry, or Holter monitoring.[4,5] Other strokes of cardioembolic origin are explained by recent myocardial infarction or valvular heart disease that not infrequently are previously known diagnoses. Some of these patients have had previous cardiological evaluations, or have suffered complex clinical conditions after their strokes or other diseases, like severe alcohol abuse, gastrointestinal ulcers, or recurrent trauma with gait instability and falls, that discourage the use of anticoagulant therapy.

Echocardiography (ECO) is usually a part of the normal study workup for ischemic brain diseases as it may detect potential sources of cerebral embolism; to what extent this test could provide additional information (AI) to the clinicians and whether any of this could help in changing the patient's management has not been evaluated in detail.

In this study we investigated whether ECO adds AI for the management of ischemic brain disease and to elucidate whether this AI was helpful in the patient's acute care.

Patients and Methods

Consecutive patients from our Registro de Enfermedades Cerebrovasculares (RECCA cohort) admitted to Clínica Alemana de Santiago, in Santiago, Chile, with acute ischemic strokes (AIS) or transient ischemic attack (TIA) aged >18 years were prospectively included between February 2013 and January 2017. When a patient with acute brain ischemic symptoms consulted at the Emergency Room (ER), the neurologist assessed demographic, clinical and risk factors. Stroke severity is assessed applying the National Institute of Health Stroke Scale (NIHSS), and for TIA the abcd2 score. Following the clinical evaluation, blood samples and ECG are obtained. Patients are then studied with a neuroimaging protocol, which has been previously described[6] consisting of a brain Computed Tomography (CT) and, in those patients without contraindications; an immediate CT angiography (CTA) of the cervical and intracranial arteries and then Diffusion Weighted Image (DWI) by Magnetic Resonance (MR). If CTA cannot be performed an acute MR angiography was performed.

Patients eligible for intravenous (IV) thrombolytic therapy were treated within a time window of 4.5 hours, with transcranial Doppler monitoring; if no recanalization by ultrasound occurs or if there is a contraindication for thrombolytic drugs, intra-arterial thrombectomy is performed.

After the acute evaluation, patients are hospitalized in the Stroke Unit, for at least 48 hours in the case of AIS, or until the etiological study is completed, and medical treatment is started in the case of TIA. Telemetry monitoring is performed in all patients, and in the first 48 hours of hospitalization, experienced cardiologists, not aware of this study, carried out a not-blinded transthoracic echocardiogram (TTE) evaluation as part of the work-up.

Echocardiographic examinations were performed with a Vivid E9 (GE Healthcare Milwaukee, EEUU) with a standardized protocol, using a M5S transducer (wide bandwidth phased array transducer; frequency band- width: 1.5-4.6 MHz). All cardiac measurements were carried out in the 2D-Mode of the parasternal long axis. Left ventricular function was evaluated in the apical 4-, 3-, and 2-chamber views and categorized by the specialist according to current recommendations.[7,8] Contrast TTE with agitated saline solution, 0.9% was performed in patients younger than 55 years, in patients of all ages with suggestion of paradoxical embolism (like long journeys in airplane or buses, or long bed rest or fractures in the lower limbs).

A transesophageal echocardiogram (TEE) was performed according to the treating vascular neurologist's opinion in patients with cardiac masses or normal findings in the TTE study but with suspected embolism or endocarditis.

Additional information provided by ECO was defined as: information generated by these evaluations only according to the attending neurologist and classified as: cardiomyopathies, left ventricular aneurysms, intra-cardiac thrombus or tumors, vegetations, aortic arch atheromatous plaques, patent foramen ovale (PFO) or intracardiac shunts, aortic arch atheromatosis, left atrial enlargement, or any other information that ECO could provide and was deemed to be useful immediately after the examination was done.[9] Changes in the management of patients stimulated by the results of ECO findings were: modifications in the volume of intravenous fluids, beginning of antibiotic, anticoagulation, or diuretics use or surgical/endovascular procedures or modifications of the studies planned and carried out as defined by the attending physician immediately after the results of the

Table 1. *Baseline characteristics of the participating patients.*

Variables	$N = 696$
Mean age, years (SD)	70 (±15.3)
Female sex (%)	399 (57.3%)
Hypertension (%)	450 (64.6%)
Diabetes mellitus (%)	255 (36.6%)
Hypercholesterolemia (%)	301 (43.2%)
Tobacco (%)	189 (27.1%)
Heart Failure (%)	84 (15.9%)
Atrial fibrillation (%)	131 (18.8%)
Coronary artery disease	111 (15.9%)
Mean time from symptom onset to ER*, minutes (SD)	830 (±1442)
Intracranial vessel occlusion	188 (27.%)
Carotid stenosis over 50%	62 (7.63%)
Ischemic Stroke	533 (76.9%)
Transient ischemic attack	163 (23.1%)
Admission NIHSS†	Mean 6 (±6.5)
ABCD2 score	Mean: 3
Ecocardiography	
Trans-thoracic	696 (100%)
Trans-esophageal	36 (5.17%)
TOAST classification	
Atherosclerotic	103 (14.8%)
Cardioembolic	182 (26.2%)
Undetermined	273 (39.3%)
Lacunar	94 (13.5%)
Other diagnosis	43 (6.2%)
Treated with	
rtPA‡	131 (18.5%)
Intra-arterial revascularization	34 (4.9%)

*ER: Emergency Room.
†National Institutes of Health Stroke Scale.
‡Intravenous thrombolysis.

echocardiography became available. At discharge patients were stratified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST).[10]

RECCA has approval by our Institutional Ethics and Scientific Committee. All patients or their relatives provided informed consent.

Analysis

The proportion of AI and the changes in management resulting from ECO were calculated with 95% confidence intervals. Univariate analysis was performed using chi square test for frequency data to study the associations of AI with age, sex, cerebrovascular risk factors, type of cerebrovascular disease (AIS versus TIA), NIHSS, the presence of intracranial occluded vessels or carotid stenosis in CTA. A logistic regression analysis was performed for those variables that were associated ($P < 0.25$) in the univariate analysis. The same analysis was performed for patients in whom AI induced changes in their management. All analyses were performed with STATA 15.

Results

Within the study period, 742 patients were admitted to our Stroke Unit with AIS or TIA; of these, 46 did not undergo ECO evaluation for the following reasons: 6 early deaths, 17 patients with severe stroke and poor prognosis, 10 patients were transferred to our hospital with ECO evaluation already done in another center, 7 cases did not consent and finally 6 were excluded for other reasons.

The baseline characteristics of the 696 patient participants are shown in Table 1. Three hundred ninty nine (57.3%) patients were female, and their mean age was 70 (±15.3) years. Patients were admitted at a mean of 830 (±1442) minutes from symptom onset and ECO was performed at a mean of 1729.8 (±1407) minutes from the cerebrovascular event. During the study period, 131 (18.5%) patients were treated with intravenous thrombolysis, which was followed by thrombectomy in 9 patients; in 2 cases this was the initial recanalization therapy.

All cases were evaluated with TTE, 17 cases (2.4%) demonstrated suboptimal sonographic windows. 36 cases (5.2%) were studied also with TEE. 31% of the ECO evaluations were considered normal while in 142 patients (20.4%, 95% CI 17.5-23.5), the ECO yielded information that was considered additional by the attending neurologist, the most frequent was the increase in the left atrial volume enlargement (Table 2). Intra-cardiac thrombi were present in only 7 (1%) of examinations while endocarditis was diagnosed in 2 patients (0.3%) and an intra-cardiac tumor was even more infrequent: 1 case (0.1%).

The univariate analysis of the association between AI and clinical radiological variables is shown in Table 3. Diabetes mellitus ($P = 0.063$), hypercholesterolemia ($P = 0.198$), AF ($P = 0.186$), previous ischemic heart disease ($P = 0.40$), admission NIHSS ($P = 0.06$), intracranial vessel occlusion ($P = 0.14$), and the presence of carotid stenosis over 50%, ($P = 0.21$), were associated with AI. The multivariate analysis, demonstrated that the presence of AF (OR: 0.37; 95% CI, 0.2-0.69), a history of ischemic heart

Table 2. *Additional information provided by ECO on 696 patients.*

Additional information	N (%)
Left atrial volume increase	50 (7.1%)
Normal ECO evaluation	29 (4.2%)
Inter auricular communication	18 (2.6%)
Acute myocardial infarct	9 (1.2%)
Cardiac valvulopathy	7 (1%)
Intracardiac thrombi	
Presence	7 (1%)
Absence	6 (0.9%)
Patent foramen ovale	6 (0.9%)
No suspected cardiac myocardiopathy	4 (0.6%)
Endocarditis vegetations	2 (0.3%)
Other findings	10 (1.4%)

Table 3. *Univariate analysis of predictors of additional information (AI) on ECO.*

Variables	AI absent, $N = 554$ (79.6%)	AI present, $N = 142$ (20.4%)	*P*
Mean age, years (SD)	70 (±14.9)	69.9 (±17.1)	0.95
Female sex (%)	322 (58.1%)	77 (54.2%)	0.34
Hypertension (%)	361 (65.1%)	89 (22.6%)	0.49
Diabetes mellitus (%)	213 (38.4%)	42 (29.5%)	0.063
Hypercholesterolemia (%)	247 (44.5%)	54 (38%)	0.198
Tobacco (%)	152 (27.4%)	37 (26%)	0.833
Heart Failure (%)	64 (11.5%)	20 (14%)	0.391
Atrial fibrillation (%)	110 (19.8%)	21(14.7%)	0.186
Coronary heart disease	80 (14.4%)	31(21.8%)	0.040
ICO[†]	140 (25.2%)	48 (33.8%)	0.104
Carotid Stenosis > 50%	47 (8.4%)	6 (4.2%)	0.21
Ischemic Stroke	422 (76.2%)	111 (78.2%)	0.578
TIA[‡]	132 (27.8%)	31 (21.8%)	
Admission NIHSS[§]	5.76 (±6.3)	6.97 (±7.3)	0.06
ABCD2 score	3(±1.2)	3 (±1.2)	0.91
Treated			
rt_PA	103	28	0.810
Intra-arterial revascularization	26	7	0.810

*ER: Emergency Room.
[†]Intracranial occlusion.
[‡]Transient ischemic attack.
[§]National Institutes of Health Stroke Scale, intravenous thrombolysis.

disease (OR: 2.31; 95% CI, 1.32-4.01), diabetes mellitus (OR: 0.54 95% CI, 0.35-0.85), carotid stenosis of over 50% (OR: 0.38; 95% CI, 0.15-0.98) and admission NIHSS (OR: 1.04; 95% CI, 1.01-1.07), were variables independently associated with AI detected by ECO.Table 4

ECO findings changed the management of 76 (10.9% CI 8.8-13.4) patients and of these, 45 (6.4% CI 4.8-8.5), were medical treatments: anticoagulation therapy, intravenous antibiotics, and adjustments of other medical therapies, including the volumes of fluids perfused, surgical, or endovascular interventions. The other changes in management were additional tests, 24-hour rhythm Holter monitoring (one demonstrating atrial fibrillation) and 7 studies for paradoxical embolism in pelvic and legs veins with three positive results. Table 5

The univariate analysis between change of management due to findings in ECO and clinical-radiological variables in the ER is shown in Table 6. Coronary heart disease ($P = 0.178$), AF ($P = 0.082$), the presence of an AIS ($P = 0.19$), and admission NIHSS ($P = 0.001$) were significantly associated. In multivariate analysis only coronary heart disease (OR: 2.64 95% CI, 1.34-5.25), AF (OR: 0.24; 95% CI, 0.2-0.69), and admission according to NIHSS criteria (OR: 1.04; 95% CI, 1.01-1.09) remained significant.Table 7

The only difference found between the findings with ECO in patients treated with Alteplase and those who did not receive this therapy was that those in the first group showed more frequently increases of the left atrial volume. ($P = 0.001$). Six of the seven intracavitary thrombi were found in patients not treated with rt_PA but these were not statistically significant P-value = 0.75.

Discussion

In this prospective study performed in non-selected consecutive patients with acute ischemic brain disease,

Table 4. *Multivariable analysis, of predictors of additional information (AI) on ECO.*

Variable	OR	95% CI	*P* Value
Diabetes mellitus	0.54	0.35-085	0.008
Hypercholesterolemia	0.93	0.57-1.52	0.78
Atrial fibrillation	0.37	0.2-0-69	0.032
Coronary heart disease	2.31	1.32-4.01	0.003
Intracranial occlusion	0.17	0.65-5.10	0.265
Carotid stenosis > 50%	0.38	0.15-0.92	0.001
Admission NIHSS*	1.04	1.01-1.07	0.007

*National Institute of Health Stroke Scale.

Table 5. *Changes in patient's management determined by ecocardiogram.*

Changes in management	*N* (%)
Begging of anticoagulation	16 (2.3%)
Valvular surgery	4 (0.6%)
Antibiotic therapy	2 (0.3%)
Other pharmacological therapies	13 (1.9%)
Influence in EV fluid therapy	7 (1%)
Coronariography and stenting	3 (0.4%)
24 hours ECG Holter monitoring	24 (3.4%)
Additional evaluations	7 (1%)

Table 6. *Univariate analysis of predictors of change in management (CM) determined by ECO.*

Variables	CM absent, *N* = 620 (89.4%)	CM present, *N* = 76 (12.2%)	*P* value
Mean age, years (SD)	70 (±15.1)	69.8 (±17.4)	0.93
Female sex (%)	355 (57.2%)	44 (57.8%)	0.71
Hypertension (%)	398 (64.2%)	52 (68.4%)	0.3
Diabetes mellitus (%)	232 (37.4%)	23 (30.2%)	0.31
Hypercholesterolemia (%)	274 (44.1%)	27 (35.5%)	0.26
Tobacco (%)	168 (27%)	21 (27.6%)	0.7
Heart failure (%)	72 (11.6%)	12 (15.7%)	0.26
Atrial fibrillation (%)	123 (19.8%)	8 (10.8%)	0.082
Coronary artery disease	95 (15.3%)	16 (21%)	0.178
Intracranial vessel occlusion	167 (26.9%)	21 (27.6%)	0.84
Carotid Stenosis > 50%	58 (9.3%)	4 (5.2%)	0.53
Ischemic stroke	481 (77.5%)	52 (68.4%)	0.191
Transient ischemic attack	141 (22.5%)	22 (31.6%)	
Admission NIHSS*	5.87 (±6.3)	7.2 (±7.3)	0.001
ABCD2 score	3.1 (±1.2)	3.1 (±1.1)	0.9

*National Institute of Health Stroke Scale.

ECO provided additional useful information in 1 out of 5 patients and induced changes in management in 1 out of 10 cases, with only 1 in 20 being therapeutic decisions.

Interestingly, the attending neurologist considered as the most frequent AI an increased left atrial volume, a condition that has been described as associated with a greater risk of recurrence of ischemic stroke[11,12], but also with more severe strokes[13] and with AF, an arrhythmia that has a high risk of stroke recurrence and which should be treated with anticoagulation.

A normal ECO was considered the second most frequent source of AI and it was important because it allowed to rule out structural heart disease as the origin of cardio-embolism, which would require a more aggressive treatment.

Thrombi of cardiac origin were identified only in 1% of ECO evaluations, a number close to those described in other studies[14,15]; this could be due to the small number of TEE, a technique that is superior to TTE for identification of cardiac embolic sources in patients with TIA or stroke[16] and to the fact that patients with AF were always evaluated with transthoracic studies.

Similar to others studies, we found intracardiac tumors in only 0.1% of ECO evaluations and endocarditis in 0.28%.[14,15]

Not surprisingly PFO was considered only occasionally as a relevant finding in this group of patients, probably due to the fact that this study was performed before the positive trials of PFO closure were published.[17-19]

Table 7. *Multivariate analysis of predictors of change in management determinate by ECO.*

Variable	OR	95% CI	*P* Value
Coronary artery disease	2.66	1.34-5.3	0.005
Atrial fibrillation	0.23	0.09-0.6	0.003
Ischemic stroke	0.85	0.39-1.84	0.69
Admission NIHSS	1.04	1.00-1.08	0.04

In contrast with previous studies, we analyzed risk factors or variables different from age[14,15] that could be associated with the presence of AI in ECO evaluations in patients with ischemic brain disease. Our multivariate analysis showed that the presence of ischemic heart disease was an antecedent that correlates with AI; this condition could determine the appearance of areas of akinesia or dyskinesia, that can decrease the ejection fraction and could limit the amount of intravenous fluids that the patient can handle, and also, significant akinesia increase the risk of ectasia with local thrombus formation and may be an indication for the use of anticoagulation.[20] Higher admission NIHSS also correlated with the AI provided by ECO, as Kimura et al,[21] reported that higher NIHSS values correlated with the presence of AF and cardio-embolism. This could lead to higher chances of abnormalities in the ECO evaluation.

On the other hand, the presence of AF in our stroke patients decreases the chance that ECO will provide AI, as this group of patients had a clear indication for anticoagulant use independently of the results of the ultrasound evaluation. The presence of carotid stenosis also decreases the probability of AI provided by ECO, as this information is provided early by our neuroimaging protocol performed in the ER. ECO probably will not add much information about the condition of these patients. In the case of Diabetes Mellitus, this disease is an independent risk factor for lacunar strokes,[22] a diagnosis that was frequently done in the ER by the DWI evaluation and that could depict this kind of stroke clearly[23] what could decrease the expectations on the results of the ECO.[24]

ECO modified the management of 10.7% of our patients, very similar to the published data by Katsanos et al.,[25] where they found with TEE, a 9.1% of treatment modification. Our results are not surprising since our data was obtained prospectively and represents not only the indication for anticoagulant therapy, that was not high, 16 (2.2%) cases, but we also measured the influence of other modifications of the treatment such as careful management of IV fluids in heart failure, use of diuretics in pulmonary hypertension or surgeries in patients with severe valvular disease, which to our knowledge had not been evaluated in detail.

Almost half of the changes in management stimulated by ECO, were related to the search for sources of emboli, like AF using rhythm Holter (positive in one case) or the search of paradoxical embolism (founded in 3 patients).

The elements that correlated with changes of management in multivariate analysis were previous ischemic heart disease, which could cause structural changes in the heart and could require more complex treatments, the presence of higher admission NIHSS that, correlates with the presence of AF and could lead to the search for this arrhythmia. The presence of AF changes the management and works, as a protective factor as for it anyway requires anticoagulant therapy irrespective of the results of ECO. Age did not affect the necessary changes in management guided by the echocardiography as published previously by Wolber et al.[14]

The main strengths of our study are that it was conducted in consecutive patients with AIS and TIA in a clinical setting, independently of their respective risk factors.

Our study also has some limitations, only a small proportion of patients received TEE evaluations, which is considered the gold standard for detection of thrombi in the left atrium or the left atrial appendage, PFO, atrial septal aneurysm, and aortic atheroma.[26,27] This could have introduced some selection bias, although this is in agreement with the 2016 ASE guideline recommendations,[28] TEE is recommended only when the results of TTE are not satisfactory and there is either a very high degree of suspicion of a cardioembolic source or the anatomy and function of the left atrium needs to be known for cardioversion, ablation, or percutaneous procedures for LAA closure. Additionally, this is a single center experience where patient evaluation and the adjudication of abnormal evaluations was not centralized and blinded; finally this investigation was completed before the publication of the REDUCE and CLOSE trials[29,30] which showed that closure of PFO decrease stroke recurrence and therefore it could have increased the percentage of changes in management and in the AI provided by ECO.

Conclusions

In unselected patients with ischemic brain disease, ECO had a low yield providing additional information, and it changed the management in a small percentage of patients.

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