Full title: ECG markers associated with ischemic stroke at young age – A case-control study

Running head: ECG markers in young stroke

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Abstract

Introduction: Certain ECG abnormalities are associated with ischemic stroke (IS), especially cardioembolic subtype. Besides atrial fibrillation, markers of left ventricular hypertrophy (LVH) or atrial pathology also reflect elevated risk. We studied the association of ECG markers with IS in young adults.

Methods: We performed a case-control study including 567 consecutive IS patients aged 15 to 49 years (inclusion period 1994-2007) and one or two age- and sex-matched control subjects enrolled during 1978 to 1980 (n=1033), and investigated also the stroke etiologic subgroups. We studied ECGs of all participants for markers of atrial abnormality, i.e. P-terminal force (PTF) on lead V1, interatrial blocks (IAB; P-wave duration ≥110 ms), and LVH. Conditional logistic regression analyses were used.

Results: IAB (hazard ratio [HR] 1.57, 95% confidence interval [CI] 1.16-2.13) and PTF combined with LVH (HR 6.83, 95% CI 1.65-28.31), were independently associated with IS. LVH, abnormal P-wave (HR 6.87, 95% CI 1.97-135.29), PTF, IAB, and combinations of these P-wave abnormalities with LVH – were associated with cardioembolic subtype. Abnormal P-wave and IAB were associated with cryptogenic stroke subtype. In unadjusted analysis, LVH was associated with small-vessel disease subtype.

Conclusions: P-wave abnormalities on ECG were associated with cardioembolic but also with cryptogenic subtype of IS.

Key words:

cardioembolism, case-control study, cryptogenic stroke, ECG, ESUS, LVH, P-wave, stroke, stroke in the young.

Key messages:

1. ECG patterns associated with atrial pathology are markers of increased risk of ischemic stroke in young adults.
2. The ECG markers reflecting atrial pathology were seen in patients with cardioembolic and cryptogenic subtypes of ischemic stroke.

Introduction

Atrial fibrillation (AF) is a well-known risk factor for ischemic stroke (IS), but apart from AF, certain other electrocardiographic (ECG) patterns have also been linked to an elevated risk of stroke (1-3). These associations are mainly due to cardiac abnormalities, and hence intuitively such ECG findings should be associated with cardioembolic stroke subtype. In fact, a prolonged P-wave was associated with cardioembolic stroke in one study (4). Also, a theory on fibrous atrial cardiopathy has emerged, proposing that unhealthy atrial substrate—regardless of the presence of AF— may predispose to thrombus formation in the left atrial appendage and left atrium hence increasing the risk of cardioembolism (5,6). In the general population, left ventricular hypertrophy (LVH) on ECG has been linked to an increased risk for IS (7).

In young population, however, few studies exist on the association between ECG abnormalities and IS. In a population of young adults with IS, we have earlier demonstrated that P-terminal force (PTF) was associated with the subtype of cardioembolism from a high-risk source (8).

One key feature differentiating young patients with IS from older patients is the higher frequency of cryptogenic strokes, i.e. strokes with undetermined etiology (9). In the case of recently proposed clinical construct—embolic strokes of undetermined source (ESUS) — clinical and radiological findings point towards embolism, but the embolic source cannot be identified (10). Based on preliminary analyses, majority of the cryptogenic strokes at younger ages may fulfill the ESUS criteria (11).

The secondary prevention of cardioembolic strokes differs markedly from other stroke etiologies. Thus, it would be of great importance to identify these patients who would be likely to benefit from thorough examinations to reveal a source of embolism. Therefore, we performed a matched case-

control study on the association of ECG markers of atrial pathology with early-onset IS. Furthermore, we aimed to study these associations in stroke etiologic subgroups, with particular interest in cardioembolism from high-risk sources and ESUS. As the markers of atrial pathology are relatively common in presumably healthy populations, we also studied whether combining LVH with these atrial markers would increase their association with IS (12).

Methods

The stroke cases came from the Helsinki Young Stroke Registry (HYSR), consisting of 1008 consecutive patients with first-ever IS at age of 15 to 49, enrolled during the period between 1994 and 2007 (13). The control subjects were obtained from the 7217 participants of the Mini-Finland Health Survey enrolled during the period from 1978 to 1980 and representing the Finnish population 30 years old and over (14). For the present study, we selected 1067 municipality-, age- and sex matched controls from those free from IS. One or two controls were selected for each HYSR patient. Municipality was matched by restriction firstly to Helsinki (65%), secondly to Turku (20%) and thirdly to other municipalities in the Southern part of Finland. Sex and age were selected by individual matching, age using nearest available matching. Age was considered matched when it was +/-5 years the age of the patient, therefore patients younger than 25 years were ruled out due to lack of control subjects. Besides the matching, the following confounding factors were considered by modeling: systolic blood pressure, diastolic blood pressure, HDL cholesterol, obesity (BMI $\geq$ 30 kg/m^2), diabetes, coronary artery disease and cigarette smoking. More detailed definitions of these factors are described in supplementary Table s1.

The ECG of stroke patients was obtained at least 1 day after, and always within 14 days of their stroke. Because our study focused on P-wave parameters, only patients and controls in sinus rhythm were selected; the Mini-Finland Health Survey persons with their studied ECG in AF were excluded from the present study. Also persons with incomplete data on the considered clinical parameters were excluded. Only the case-control sets containing complete data of the aforementioned factors in the case and one control were included. A total of 567 stroke patients (63.5% male) and 1033 matched controls had complete data on all the studied variables, and were in sinus rhythm, and were included in the present study. $CHADS_2$ and CHA_2DS_2-VASc scores were calculated for the stroke patients, according to established criteria (15,16).

The study was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa (no. 73/13/03/00/11) and by the National Institute of Health and Welfare (THL).The Mini-Finland Health Survey preceded the current legislation on ethics in medical research. All participants were fully informed about the study, they participated in the study voluntarily and the use of the information for medical research was explained to them. Agreeing to participate in the baseline health examination was taken to indicate informed consent. Record linkage of national health registers to the survey data has been approved by the register authorities.

Stroke subtype definitions

Stroke subtypes were initially classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (17). Among the cryptogenic cases (TOAST 5), we further classified those with ESUS according to the recently proposed criteria as non-lacunar stroke detected by CT or MRI; absence of extracranial or intracranial atherosclerosis causing 50% luminal stenosis in arteries supplying the ischemic area; absence of a major-risk cardioembolic source of embolism; and absence of any other specific cause of index stroke (10). In our study, AF was systematically searched either with 24-48-hour Holter ambulatory ECG monitoring, repeated ECGs during hospitalization, or continuous ECG-monitoring in emergency unit or acute stroke unit. At least transthoracic echocardiography was performed for all stroke patients in the ESUS group. Arterial imaging was done either by CTA, MRA, or ultrasound imaging. We classified patients with an incomplete diagnostic work-up in the non-ESUS cryptogenic group, as we did with patients not fulfilling the other ESUS criteria.

Cardioembolism was defined as the stroke being clinically embolic, and the source was atrial fibrillation or flutter, dilated cardiomyopathy, recent myocardial infarction, congenital heart disease,

infective endocarditis, mechanical aortic valve, congestive heart failure, thrombotic endocarditis, or atrial myxoma (18).

ECG analysis

All ECG recordings of both patients and controls were registered as standard 12-lead ECGs with 50 mm/s speed and 0.1 mV/mm amplitude while the subjects rested in supine position. Parameters analyzed manually from the ECGs (by authors J.Pi and A.E) were P-wave duration, PTF (negative terminal P-wave deflection in lead V1 ≥ 0.1 mV and ≥ 40 ms duration, early positive part not considered, Figure 1), biphasic P-waves in inferior leads and LVH by either Sokolow-Lyon or Cornell Voltage duration criteria (1,19,20). First-degree interatrial block (IAB) was defined as P-wave duration ≥110 ms and third-degree IAB as a P-wave duration of ≥110 ms and biphasic P-waves in at least two inferior limb leads (21). P-waves were considered abnormal when either IAB of first or third degree or PTF was present.

Statistical analysis

The strengths of association between markers of atrial abnormalities and IS occurrence were estimated using conditional logistic regression. Odds ratios and 95 % confidence intervals were calculated for the markers, and intervals not crossing the value 1.00 were considered significant. Analyses were first performed in the entire population, adjusting for clinical variables satisfying criteria for confounding. The models thus consisted of systolic blood pressure, diastolic blood pressure, HDL cholesterol, obesity, diabetes, coronary artery disease and cigarette smoking, and an ECG variable. Each ECG variable was tested in a separate model. Since the confounding factors varied from one subgroup to another, each subgroup analysis thus had a unique set of adjusted variables (Table s2). Control group in the subgroup analyses consisted of only the corresponding

controls for the cases in question. All analyses were performed on IBM SPSS 22.0 (Armonk, N.Y., USA).

Results

Descriptive data on clinical variables of patients and controls are shown in Table 1. Of the patients, 6.5% suffered their stroke due to large-artery atherosclerosis (LAA), 14.8% due to small-vessel disease (SVD), 9.0% due to cardioembolism (CE), 27.3% due to rare causes, 28.6% due to ESUS, and 13.8% were cryptogenic other than ESUS. Stroke patients had their ECG obtained at a median of 2 days (interquartile range 1-3 days) after stroke.

Stroke patients had a median $CHADS_2$ score of 2 points (interquartile range 2-3) and a median CHA_2DS_2-VASc score of 3 (interquartile range 2-4). The cardioembolism patients had a median $CHADS_2$ of 3 (interquartile range 2-4) and a median CHA_2DS_2-VASc score of 4 (interquartile range 3-5).

Of the cardioembolism patients, two used warfarin prior to stroke, and seven were on antiplatelet therapy. Nine cardioembolism patients were known to suffer from AF, and more detailed data on cardioembolic sources are found in Table s3.

Association of ECG findings, clinical parameters and stroke in the entire population

Correlations between clinical variables and ECG parameters are shown in supplementary Table s4. The prevalence of different ECG abnormalities in the controls and the etiological subgroups of stroke patients are displayed in Table 2. After multivariate adjustment, the parameters independently associated with stroke of any kind were first-degree IAB, PTF in combination with LVH, abnormal P-waves, and abnormal P-waves in combination with LVH (Table 3).

Association of ECG findings according to stroke subtype

Since the third-degree IAB was too scarce for analysis in the subgroups, third-degree IAB and its combination with LVH were not included in the subgroup analyses. LVH, first-degree IAB, first-degree IAB combined with LVH, PTF, PTF combined with LVH, abnormal P-wave and abnormal P-wave combined with LVH were independently associated with cardioembolism stroke subtype (Table 4). LVH was associated with SVD, although only in the univariate analysis (Table s5). First-degree IAB and abnormal P-wave were associated with non-ESUS cryptogenic stroke subtype. (Supplementary Table s2).

Discussion

Our main result is that in our cohorts of young stroke patients and their age- and sex-matched controls, LVH and several abnormal P-wave parameters were independently associated with cardioembolic stroke subtype, while the only other subgroup associated with P-wave abnormalities was the non-ESUS cryptogenic group. We also found LVH associated with SVD.

In recent years, the role of atrial fibrillation as a risk factor for cardioembolic stroke has expanded from arrhythmia, causing stasis and thrombus formation in the left atrial appendage, to a marker of fibrotic atrial cardiopathy. In fibrotic atrial cardiopathy, the fibrosis disrupts atrial electrical conduction properties, predisposing to re-entry and proliferation of ectopic foci promoting atrial fibrillation, whereas inflammation, endothelial dysfunction, and atrial hypocontractility promote thrombus formation (6,22). P-wave duration is a crude marker of atrial electrical conduction properties. PTF serves relatively well as a marker of left atrial dilatation, but it can be caused also by impaired interatrial conduction and especially of elevated left atrial pressure (23,24). The subacute setting of stroke is probably not the cause of PTF per se, and the patients were already in

hospital treatment and therefore possible cases of cardiac decompensation were probably already treated. Both prolonged P-wave duration and PTF have been associated with increased risk of developing AF (25,26). Thus, the large prevalence of these abnormalities especially in stroke patients is not surprising. It was recently shown that both PTF and advanced (third-degree) IAB were associated with IS in large multiracial general population cohorts even after accounting for the presence of atrial fibrillation (2,3). We also found that PTF and first-degree IAB were associated with cardioembolic stroke, although our cases with third-degree IAB were too few for analyses. This is an interesting and novel finding, as in young stroke patients, the causes of cardioembolism are markedly more diverse than in older population. However, the presence of P-wave abnormalities in an ECG of a young stroke patient should encourage the clinician to think of the possibility of cardioembolism.

Of special interest would be, whether the ESUS or cryptogenic stroke subgroups would share similar ECG abnormalities as the cardioembolism subgroup, and thus suggest a common pathogenesis of stroke in these groups. A positive, inconclusive trend of PTF associated with the risk of cryptogenic stroke was found in a case-control study of markedly older stroke patients, although in general, PTF was associated with stroke (27). Another study found PTF to be associated with non-lacunar strokes independently of AF (28). We found novel associations between first-degree IAB and P-wave abnormalities with non-ESUS cryptogenic stroke, although weaker than with cardioembolism. In older patients, ECG markers of left atrial abnormality have been found to be independent risk markers for IS even when considering echocardiographic parameters (29). The theory of fibrotic atrial cardiopathy, as described earlier, is receiving more evidence, although the mechanisms of cryptogenic strokes and ESUS may be different in young and old patients.

Both PTF and increased P wave duration are markers of atrial pathology; however, the prevalence

of these markers is relatively high also among subjects free of apparent cardiac disease (12,26). Thus, we assumed that using a combination of markers of atrial pathology and LVH would be a more specific indicator of significant cardiac pathology, and thus a stronger risk marker. Based on an earlier study, there might be a synergy in stroke risk between atrial ECG abnormalities and LVH on ECG. In that study, including 55-60-year-old patients, it was found that an abnormal P-wave increased the risk of stroke in a cohort of patients with LVH (30). Pathophysiologically atrial abnormality on ECG, indicating left atrial pressure overload, could also be viewed as a marker of systolic or diastolic dysfunction of the left ventricle, reflecting more severe heart disease than isolated LVH alone (31). We found LVH with P-wave abnormalities associated with cardioembolic stroke, as did LVH per se LVH was also associated with SVD in our univariate analysis (Table s5). SVD is strongly associated with diabetes, and the finding could reflect a recent finding of type 2 diabetes being a risk factor for LVH, independent of hypertension (32). We also found diabetes significantly correlating with LVH, and the higher amount of diabetes type 2 in the SVD subgroup could explain LVH being associated with SVD (Table s4). Although patients with small-vessel disease as their etiology had the highest frequency for arterial hypertension (85%), PTF was overrepresented only in the cardioembolism group but not in SVD group, indicating PTF is a sign of major changes in cardiac structure and electric function rather than early cardiac stress due to hypertension.

Our study has strengths and limitations. The main limitation is the time difference in enrollment of the case- and control cohorts. Since blood pressure levels might be different between the time periods, namely higher in general population during the control population's era, the prevalence of LVH could be overestimated in our control population. Other limitations include the relatively small numbers of patients in etiologic subgroups, the low prevalence of certain studied ECG markers, and the lack of AF data in control subjects. The confidence intervals in some subgroup

analyses apart from cardioembolism were broad, and type 2 errors cannot be ruled out. Strengths include the case- and control populations being from the same region and a large number of young patients with IS in the stroke cohort. The lack of echocardiography data can also be considered a limitation, although there is also value in knowing what ECG can tell regardless of echocardiographic findings.

Conclusions

We found that PTF and first-degree IAB were associated with IS in young adults. With further analysis in subgroups, we observed that this association applied only to cardioembolic and non-ESUS cryptogenic subtype.

Declaration of interest and funding

Jani Pirinen is working for GE Healthcare as principal investigator in an ECG-device related research and development project. The study was funded by Helsinki University Hospital District research funds (EVO), grant number TYH2015120 and the Finnish Cardiovascular Research Foundation (Sydäntutkimussäätiö). Jani Pirinen also received a grant from the Greta and Alfred Runeberg Foundation, Finska Läkaresällskapet, the Finnish Medical Foundation (Suomen Lääketieteen Säätiö), the Maire Taponen Foundation, Svenska Kulturfonden and HUS Medical Imaging Center for this work. Antti Eranti received grants from the Finnish Medical Foundation, the Veritas Foundation and the Orion Research Foundation.

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Figure and table legends

Figure 1. Sample cardiac cycles of studied ECG parameters. Panel a) first-degree IAB (P-wave duration >110 ms, without positive-negative morphology in inferior leads), b) third-degree IAB (P-wave duration >110 ms, positive-negative morphology can be seen in leads II, aVF and III), c) PTF (negative terminal part of P-wave in V1 >40 ms duration and deeper than -1.0 mm).

Table 1. Demographics, blood pressure, cholesterol and comorbidities in cases and controls. Numbers are median (interquartile range) for continuous parameters and n (%) for dichotomous parameters.

Table 2. Prevalence of different ECG abnormalities in stroke etiologic subgroups and controls. Numbers are n (%).

Table 3. ECG abnormality differences between cases (N=567) and controls (N=1033). Conditional logistic regression adjusted for systolic blood pressure, diastolic blood pressure, HDL cholesterol, obesity, diabetes, coronary artery disease and cigarette smoking. In P-wave parameter-LVH combinations, the reference group is those having neither abnormality.

Table 4. Conditional logistic regression analysis on the ECG abnormalities associated with cardioembolic stroke subtype (N=51). Model adjusted for diastolic blood pressure and HDL cholesterol. As controls for the cardioembolism patients, only the defined as the control population for the cardioembolism patients are used (N=87).

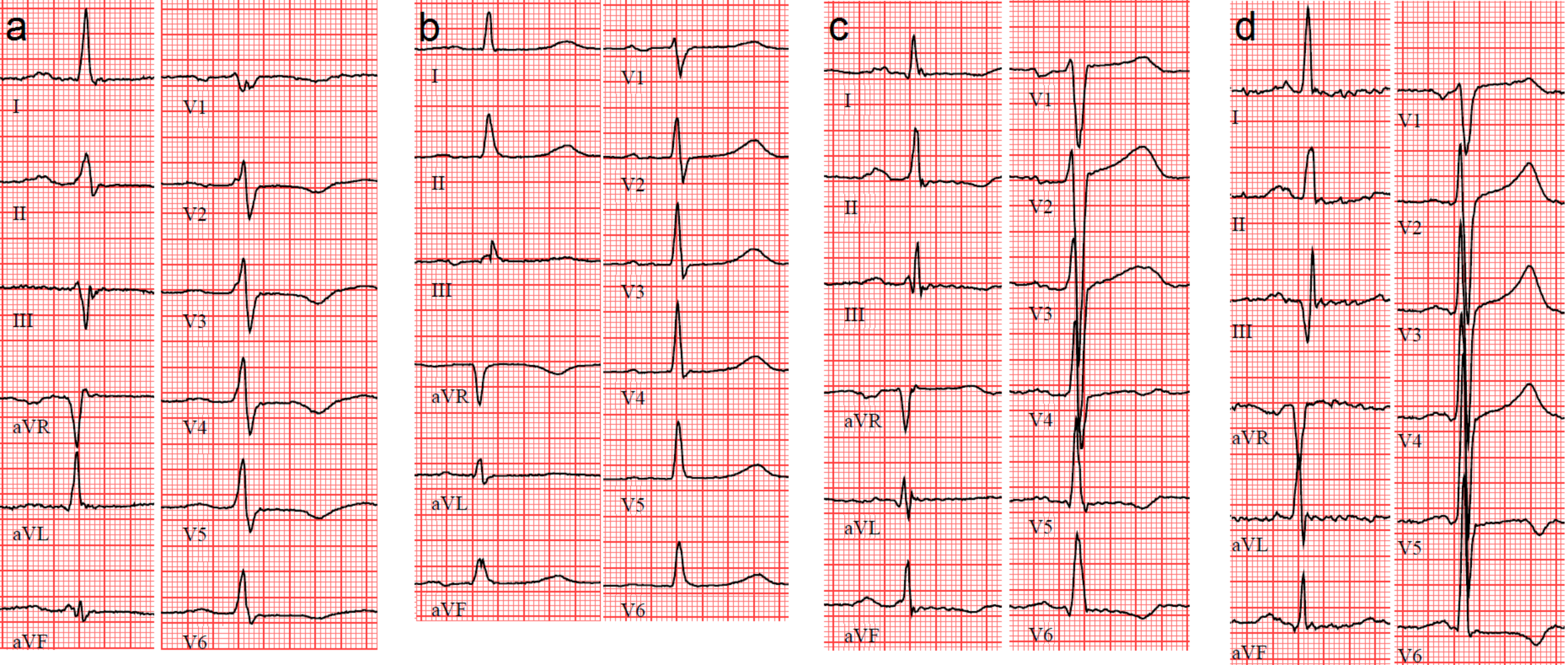
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Table 1.

Parameter	**Cases** **N= 567**	**Controls** **N= 1033**
Age	44 (37-47)	43 (38-47)
Systolic blood pressure, mmHg	140 (125-156)	134 (125-145)
Diastolic blood pressure, mmHg	84 (75-94)	88 (81-95)
HDL cholesterol, mmol/L	1.3 (1.1-1.6)	1.7 (1.4-1.9)
Obesity	62 (11)	115 (11)
Diabetes	64 (13)	11 (1)
Coronary artery disease	27 (5)	14 (1)
Cigarette smoking	256 (45)	329 (32)

Table 2.

ECG abnormality	LAA N=37	CE N=51	SVD N=84	Rare causes N=155	ESUS N=162	Non-ESUS Cryptogenic N=78	Controls N=1033
LVH regardless of other ECG findings	13 (35.1)	24 (47.1)	23 (27.4)	28 (18.1)	24 (14.8)	11 (14.1)	183 (17.7)
First-degree IAB	10 (27.0)	30 (58.8)	30 (35.7)	46 (29.7)	49 (30.2)	23 (29.5)	296 (28.7)
First-degree IAB and LVH	7 (18.9)	13 (25.5)	9 (10.7)	9 (5.8)	9 (5.6)	6 (7.7)	62 (6.0)
P-terminal force	1 (2.7)	15 (29.4)	1 (1.2)	4 (2.6)	0	1 (1.3)	31 (3.0)
P-terminal force and LVH	1 (2.7)	7 (13.7)	0	4 (2.6)	0	1 (1.3)	7 (0.7)
Abnormal P-wave	13 (35.1)	34 (66.7)	33 (39.3)	51 (32.9)	56 (34.6)	26 (33.3)	342 (33.1)
Abnormal P-wave and LVH	8 (21.6)	15 (29.4)	10 (11.9)	12 (7.7)	10 (6.2)	7 (9.0)	71 (6.9)
Third-degree IAB	3 (8.1)	1 (2.0)	2 (2.4)	3 (1.9)	7 (4.3)	3 (3.8)	29 (2.8)
Third-degree IAB and LVH	2 (5.4)	0	1 (1.2)	1 (0.6)	1 (0.6)	1 (1.3)	7 (0.7)

LAA = large-artery atherosclerosis, SVD = small-vessel disease, CE = cardioembolism, ESUS = embolic stroke of undetermined source.

LVH = left ventricular hypertrophy, IAB = interatrial block.

Table 3.

ECG abnormality	Odds ratio (95% confidence interval)
LVH regardless of other ECG findings	1.31 (0.91-1.87)
First-degree IAB	1.57 (1.16-2.13)
First-degree IAB and LVH	1.81 (0.06-3.09)
P-terminal force	1.14 (0.50-2.59)
P-terminal force and LVH	6.83 (1.65-28.31)
Abnormal P-wave	1.52 (1.28-2.05)
Abnormal P-wave and LVH	1.80 (1.09-2.96)
Third-degree IAB	1.02 (0.47-2.20)
Third-degree IAB and LVH	0.68 (0.16-2.84)

LVH = left ventricular hypertrophy, IAB = interatrial block.

Table 4.

ECG abnormality	**Odds ratio (95% confidence interval)**
LVH regardless of other ECG findings	3.01 (1.01-8.95)
First-degree IAB	5.40 (1.61-18.13)
First-degree IAB and LVH	5.18 (1.16-23.18)
P-terminal force	31.92 (3.27-311.16)
P-terminal force and LVH	46.96 (2.65-832.92)
Abnormal P-wave	4.96 (1.53-16.05)
Abnormal P-wave and LVH	5.63 (1.37-23.23)

LVH = left ventricular hypertrophy, IAB = interatrial block.

Online-only data supplement

Table s1. Definitions of the clinical parameters.

Parameter	**Cases**	**Controls**
Systolic blood pressure	Systolic blood pressure on admission or 24 h after admission; mean of both when available	Mean of systolic blood pressure measured after 5 minutes of rest and 1½ minutes after the first measurement
Diastolic blood pressure	Diastolic blood pressure on admission or 24 h after admission; mean of both when available	Mean of diastolic blood pressure measured after 5 minutes of rest and 1½ minutes after the first measurement
HDL cholesterol	Blood sample 24-72 hours after admission	Blood sample at health examination*
Obesity	Body mass index ≥30 kg/m^2	Body mass index ≥30 kg/m^2
Diabetes	Fasting plasma glucose ≥7.0 mmol/l (126 mg/dL) or plasma glucose after ingestion of 75 g oral glucose ≥11.1 mmol/l (200 mg/dL), with or without insulin dependence (WHO criteria)	Diagnosis of either type 1 or type 2 diabetes at the time of evaluation; only fasting glucose was measured from all participants
Coronary artery disease	Coronary artery disease diagnosed before the stroke; previous myocardial infarction, or a positive result in diagnostic methods such as perfusion imaging, coronary angiography or exercise ECG	Diagnosis of coronary artery disease at the time of evaluation; previous myocardial infarction, or a positive result in diagnostic methods such as perfusion imaging, coronary angiography or exercise ECG
Cigarette smoking	Smoking at least one cigarette per day within one year before the stroke	Smoking cigars, pipe or at least one cigarette every or almost every day within one year before the comprehensive clinical examination including ECG

*All cholesterol measurements of control subjects were performed using the Lieberman-Buchard method.[1] HDL was measured from the supernatant after precipitation with Mg++/dextran sulphate.[2,3]

Table s2. ECG abnormality differences between controls and cases of different stroke etiologies (for CE, see Table 4). Each patient group was adjusted for the parameters found associated with stroke in univariate analysis (P<0.10). LAA was adjusted for smoking, systolic blood pressure, diabetes and HDL cholesterol. SVD was adjusted for smoking, systolic blood pressure, obesity, coronary artery disease and HDL cholesterol. Etiology of rare causes was adjusted for systolic blood pressure, diastolic blood pressure, diabetes and HDL cholesterol. ESUS was adjusted for smoking, diastolic blood pressure and HDL cholesterol. Cryptogenic stroke was adjusted for smoking, diastolic blood pressure, diabetes and HDL cholesterol. Numbers are odds ratio in comparison to controls and 95 % confidence interval.

ECG abnormality	**LAA N=37**	**SVD N=84**	**Rare causes N=155**	**ESUS N=162**	**Non-ESUS cryptogenic N=78**
LVH regardless of other ECG findings	0.49 (0.11-2.25)	1.66 (0.69-4.03)	1.30 (0.60-2.79)	1.12 (0.59-2.14)	1.33 (0.49-3.65)
First-degree IAB	1.56 (0.32-7.71)	1.06 (0.52-2.14)	1.76 (0.92-3.35)	1.36 (0.81-2.28)	3.83 (1.47-9.98)
First-degree IAB and LVH	2.05 (0.28-14.94)	0.74 (0.23-2.41)	1.55 (0.44-5.51)	1.56 (0.58-4.17)	2.70 (0.55-13.23)
P-terminal force	0.02 (0.00-20.69)	0.24 (0.02-3.19)	0.46 (0.05-3.90)	-	0.28 (0.01-15.47)
P-terminal force and LVH	0.02 (0.00-20.54)	-	2.61 (0.16-42.50)	-	2.10 (0.01-478.26)
Abnormal P-wave	0.57 (0.11-2.85)	0.88 (0.43-1.78)	1.64 (0.86-3.11)	1.34 (0.80-2.26)	2.84 (1.23-6.56)
Abnormal P-wave and LVH	1.78 (0.25-12.90)	1.03 (0.32-3.29)	1.16 (0.34-3.89)	1.50 (0.60-3.80)	2.28 (0.57-9.20)

LAA = large-artery atherosclerosis, SVD = small-vessel disease, CE = cardioembolism, ESUS = embolic stroke of undetermined source.

LVH = left ventricular hypertrophy, IAB = interatrial block.

Table s3. Cardiac diseases of patients with cardioembolic stroke.

Cardiac disease	Number of patients (%)
Cardiomyopathy	18 (35)
Atrial fibrillation of flutter	9 (18)
Myocardial infarction/left ventricular thrombus	7 (14)
Endocarditis	5 (10)
Congenital cardiac malformations	4 (8)
Congestive heart failure	3 (6)
Mechanical valve	3 (6)
Myxoma	2 (4)

Table s4. Pearson correlations between clinical parameters and ECG findings. P-values >0.05 are considered not significant (n.s.). The $CHADS_2$ and CHA_2DS_2-VASc scores are calculated from stroke patients data only, since vascular disease and congestive heart failure were not well documented in control subjects.

	LVH	1° IAB	1°IAB & LVH	PTF	PTF & LVH	Abnormal P-wave	Abnormal P-wave & LVH	3°IAB	3°IAB & LVH
Sex*	-0.21	-0.15	-0.12	n.s.	-0.06	-0.18	-0.14	-0.07	n.s.
Age	n.s.	0.14	0.06	0.06	n.s.	0.17	0.08	0.06	0.06
Smoking	n.s.	n.s.	-0.05	n.s.	n.s.	n.s.	-0.06	n.s.	-0.05
Systolic blood pressure	0.23	0.12	0.17	0.08	0.12	0.15	0.20	0.08	0.13
Diastolic blood pressure	0.19	0.16	0.16	0.06	0.10	0.18	0.18	0.10	0.11
Obesity	-0.05	0.07	n.s.	0.06	n.s.	0.12	n.s.	0.10	n.s.
Coronary artery disease	n.s.	n.s.	0.06	0.10	0.05	0.07	0.08	0.09	0.07
Diabetes	0.06	n.s.	0.05	0.09	0.11	n.s.	0.07	n.s.	0.08
HDL level	-0.05	-0.08	-0.07	n.s.	n.s.	-0.12	-0.08	-0.11	n.s.
$CHADS_2$ score	0.26	0.12	0.20	0.27	0.24	0.17	0.25	0.08	0.15
CHA_2DS_2-VASc score	0.18	n.s.	0.13	0.28	0.22	n.s.	0.17	n.s.	n.s.

*Positive correlation indicates correlation with female gender

LVH = left ventricular hypertrophy, IAB = interatrial block, PTF = P-terminal force.

Table s5. Univariate conditional logistic regression analysis on the ECG abnormalities associated with stroke subtypes. Numbers are odds ratio in comparison to controls and 95 % confidence interval.

ECG abnormality	**LAA N=37**	**CE N=51**	**SVD N=84**	**Rare causes N=155**	**ESUS N=162**	**Non-ESUS cryptogenic N=78**
LVH regardless of other ECG findings	1.75 (0.69-4.49)	2.79 (1.22-6,34)	2.13 (1.10-4.14)	1.21 (0.68-2.16)	0.71 (0.41-1.25)	0.79 (0.36-1.74)
First-degree IAB	0.85 (0.38-1.89)	3.97 (1.74-9.05)	1.01 (0.59-1.74)	1.28 (0.79-2.05)	1.31 (0.83-2.05)	1.23 (0.64-2.35)
First-degree IAB and LVH	2.22 (0.74-6.63)	4.21 (1.47-12.07)	1.67 (0.65-4.30)	1.56 (0.63-3.90)	0.97 (0.43-2.20)	1.00 (0.32-3.17)
P-terminal force	0.59 (0.05-7.43)	12.89 (2.93-56.74)	0.40 (0.05-3.42)	1.16 (0.32-4.22)	-	0.35 (0.04-3.36)
P-terminal force and LVH	1.00 (0.05-18.91)	12.15 (1.48-99.53)	-	4.00 (0.73-21.84)	-	2.00 (0.13-31.98)
Abnormal P-wave	0.88 (0.40-1.91)	4.83 (2.06-11.37)	1.04 (0.61-1.77)	1.25 (0.79-1.98)	1.22 (0.79-1.89)	1.12 (0.61-2.06)
Abnormal P-wave and LVH	2.34 (0.80-6.85)	4.99 (1,79-13.98)	1.89 (0.75-4.73)	1.60 (0.71-3.63)	0.92 (0.42-2.02)	1.00 (0.35-2.83)

LAA = large-artery atherosclerosis, SVD = small-vessel disease, CE = cardioembolism, ESUS = embolic stroke of undetermined source.

LVH = left ventricular hypertrophy, IAB = interatrial block.

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