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CLINICAL RESEARCH

Impact of access route to the left ventricle on asymptomatic periprocedural brain injury: the results of a randomized trial in patients undergoing catheter ablation of ventricular tachycardia

Eva Borišincová *, Petr Peichl, Dan Wichterle, Marek Šramko, Bashar Aldhoon, Janka Franeková, Robert Čihák, and Josef Kautzner

Department of Cardiology, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, 140 21 Prague, Czech Republic

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Aims Catheter ablation of ventricular tachycardia (VT) is an effective treatment in patients with structural heart disease (SHD) and recurrent arrhythmias. However, the procedure is associated with the risk of complications, including both manifest and asymptomatic cerebral thromboembolic events. We hypothesized that periprocedural asymptomatic brain injury (ABI) can be reduced by using transseptal instead of the retrograde access route to the left ventricle (LV).

Methods and results Consecutive patients undergoing VT ablation for SHD were randomized 1:1 to either retrograde or transseptal LV access. All patients underwent radiofrequency ablation in conscious sedation with the use of an irrigated tip catheter. The degree of brain damage was evaluated by serum level of biomarker S100B. Significant ABI was defined as a post-ablation relative increase of S100B level >30%. A total of 144 patients (66 ± 9 years; 14 females; 90% coronary artery disease; LV ejection fraction: 30 ± 8%) were enrolled and 72 were allocated to each study groups. Symptomatic neurological complication of the procedure was not observed in any subject. A significant ABI was detected in 19.4% of patients. It was more commonly observed in subjects randomized to retrograde vs. transseptal LV access (26.4% vs. 12.5%, $P = 0.04$). In a multivariate analysis, only retrograde LV access and advanced age were independent determinants of significant ABI.

Conclusion Significant ABI after ablation of VT in patients with SHD can be detected in one-fifth of subjects. Retrograde access to LV is associated with a two-fold higher probability of significant ABI.

Keywords Ventricular tachycardia • Catheter ablation • Complications

Introduction

Catheter ablation is an effective treatment option for recurrent ventricular tachycardia (VT) in patients with structural heart disease (SHD). One of the most devastating complications of this procedure is cerebral thromboembolism. Although the incidence of periprocedural stroke associated with VT ablation is low,[1,2] a certain proportion of events may be silent. Previous studies have evaluated the occurrence of asymptomatic brain injury (ABI) after catheter ablation of atrial fibrillation[3,4] using diffusion-weighted magnetic resonance imaging (MRI) and/or transcranial measurement of cerebral microembolic signals.[5] We have previously shown that assessment of biomarker S100B may be used as an alternative diagnostic method for the detection of periprocedural cerebral injury.[6] In a recent study

* Corresponding author. Fax: +420 261 362 982. *E-mail address:* bore@ikem.cz

What's new?

- Periprocedural brain injury can be detected in one-fifth of patients with structural heart disease undergoing ventricular tachycardia ablation at left ventricular endocardium under conscious sedation.
- Retrograde compared with transseptal left ventricular access showed a two-fold higher probability of significant brain damage.

by Whitman *et al.*,[7] catheter ablation of VT was associated with detectable ABI in 58% of patients. The risk factors responsible for these events are speculative.

In the current study, we investigated whether the degree of periprocedural brain injury in patients with SHD undergoing catheter ablation of VT will differ with respect to the access route to the left ventricle (LV). Specifically, we hypothesized that ABI can be reduced using transseptal instead of retrograde LV access.

Methods

Study protocol

Patients referred for radiofrequency (RF) catheter ablation of VT were recruited in the period between September 2013 and March 2017. The presence of SHD with presumable LV endocardial arrhythmogenic substrate was the main inclusion criterion. Patients were excluded in case of a mechanical valve in either a mitral or aortic position that would preclude random assignment of LV access route. We did not enrol patients scheduled for pericardial access as well as those with suggestive LV outflow tract substrate, which would likely require a retrograde access. Patients with other (non-procedural) conditions that may result in the cerebral lesion (e.g. after cardiopulmonary resuscitation or recent ablation) or interfere with laboratory diagnostics (significant renal disease) were also excluded. Eligible patients were assigned to two treatment groups (retrograde or transseptal LV access) in 1:1 fashion by covariate-adaptive randomization algorithm considering age, gender, LV ejection fraction, and serum creatinine level.

Evaluation of brain injury

Peripheral venous blood sampling for assessment of protein S100B was performed immediately before the ablation procedure and in the morning on the next day. Serum samples were stored at −70°C for batch analysis by a commercially available electrochemiluminescence immunoassay (Elecsys S100 R, Roche Diagnostics, Mannheim, Germany). The test can detect protein S100B concentrations ranging from 5 to 39,000 ng/L with inter- and intra-assay coefficient of variation of 5.6% and 2.3%. Significant ABI was defined as a post-ablation relative increase of S100B level >30%.

Periprocedural anticoagulation management

In all patients with long-term anticoagulation therapy, the procedure was performed after temporary interruption of warfarin therapy, which was bridged by low-molecular-weight heparin. Direct oral anticoagulants were used only in a minority of patients in the study and if so, the treatment was interrupted 24–48 h prior to the procedure according to the renal function. In patients on antiplatelet therapy, no changes were made.

After achieving the vascular access, loading dose of unfractionated heparin (10,000 IU) was given (in case of transseptal LV access, 5000 IU prior and 5000 IU immediately after the puncture). Then, heparin was administered by intermittent boluses to maintain the activated clotting time (ACT) in the range of 300–350 s. The ACT was checked by Hemochron ACT+ (Accriva Diagnostics, San Diego, CA, USA) at 15-min intervals until therapeutic anticoagulation was achieved, and then every 15–30 min for the duration of the procedure. For purpose of the study, the mean and minimum ACT during the procedure was calculated. The mean time-weighted ACT (i.e. more representative index reflecting variable intervals between ACT sampling) was also computed.

After the ablation procedure and removal of sheaths, all patients received an infusion of unfractionated heparin with a target activated partial thromboplastin time ratio of 1.5–2.5. The next day after venous blood sampling for the assessment of S100B patients received either antiplatelet therapy for a minimum of 6 weeks or anticoagulation therapy for 3 months in case of an extensive ablation in the LV.

Catheter ablation procedure

The procedure was performed in conscious sedation using midazolam and alfentanil. Vascular access was achieved without ultrasound guidance. Mapping and ablation strategy was described elsewhere.[2] Briefly, if the VT did not occur spontaneously, the programmed stimulation protocol from the two right ventricular sites and up to three extrastimuli was applied to induce clinical VT. The mapping was performed under fluoroscopy guidance and with a three-dimensional electroanatomical mapping system (CARTO, Biosense Webster, Diamond Bar, CA, USA). The use of intracardiac echocardiography (ICE) was at the discretion of the operator. For ablation, a 3.5 mm, saline-irrigated tip ablation catheter (Navistar Thermocool, Biosense Webster) was used.

Left ventricle access (retrograde vs. transseptal) was obtained based on the randomization. Intracardiac echocardiography was used for the guidance of transseptal puncture in all cases. Substrate mapping was used in the majority of cases and was performed during the spontaneous rhythm and/or during right ventricular pacing. It predominantly consisted of sequential point-by-point bipolar voltage mapping with ablation catheter, tagging of late potentials or local abnormal ventricular activity regions, and pacing from different sites with a minimum output to assess slow ventricular conduction and morphology of the resulting QRS complex. No multipolar mapping catheter was used in the study. In patients with haemodynamically tolerated or incessant VT, three-dimensional activation mapping was initiated during tachycardia and entrainment manoeuvres were utilized. Subsequently, substrate mapping/ablation was finalized after abolition of clinical VT.

Ablation was performed in power control mode with an irrigation flow of 30 mL/min. Power was set up to 20–45 W, depending on location and catheter contact, and was down-regulated in case of catheter tip temperature rise above 43°C or rapid drop of impedance (>10–15 Ω) during ablation. Whenever ICE was used during the procedure, it was used to monitor RF delivery and prevent tissue overheating and steam pop. Radiofrequency current was applied in the majority of cases for a maximum of 60 s per target site. Pacing at 10 mA was used after RF delivery to verify non-capture at a given site. Catheter ablation was performed to abolish all inducible monomorphic VTs.

Study follow-up

The dedicated institutional tracking system was used to identify all complications during the procedure and within the minimum 3-month follow-up.

Table 1 The baseline and procedural characteristics

	Retrograde access	Transseptal access	*P*-value
Male (%)	88.9	91.7	0.57
Age (years)	65.9 ± 7.5	66.9 ± 9.7	0.52
BMI (kg/m^2)	29.7 ± 4.6	29.6. ± 5.5	0.96
Hypertension (%)	86.1	75.0	0.14
Diabetes (%)	37.5	38.9	1.00
Previous stroke/TIA (%)	4.2	18.1	0.02
Coronary artery disease (%)	87.5	91.7	0.59
LVEF (%)	30.4 ± 9.3	29.8 ± 7.4	0.67
CHA_2DS_2-VASc score	4.0 ± 1.2	4.3 ± 1.5	0.24
ICD (%)	86.1	94.4	0.16
Atrial fibrillation (%)	33.3	44.4	0.23
Warfarin (%)	37.5	50.0	0.18
NOAC (%)	8.3	4.2	0.49
Antiplatelet therapy (%)	55.6	52.8	0.87
Serum creatinine (μmol/L)	112.7 ± 31.7	112.0 ± 30.9	0.89
Radiofrequency time (min)	31.8 ± 15.7	30.1 ± 13.3	0.49
Procedure time (min)	187 ± 44	182 ± 48	0.47
Procedural DC shocks (*n*)	0.5 ± 0.8	0.5 ± 0.9	0.84
Activation mapping of VT (%)	25.0	20.8	0.55
Mean power (W)	28.8 ± 3.5	29.9 ± 2.4	0.06
Pre-procedural INR	1.22 ± 0.26	1.48 ± 0.57	0.12
Heparin dose (1000 IU)	23.0 ± 6.8	19.9 ± 6.3	0.006
Mean ACT (s)	308 ± 33	320 ± 25	0.05
Minimum ACT (s)	239 ± 49	255 ± 45	0.04
Mean time-weighted ACT (s)	314 ± 32	326 ± 23	0.05

ACT, activated clotting time; BMI, body mass index; DC, direct current; ICD, implantable cardioverter-defibrillator; INR, international normalized ratio; LVEF, left ventricular ejection fraction; NOAC, new oral anticoagulant; TIA, transient ischaemic attack; VT, ventricular tachycardia.

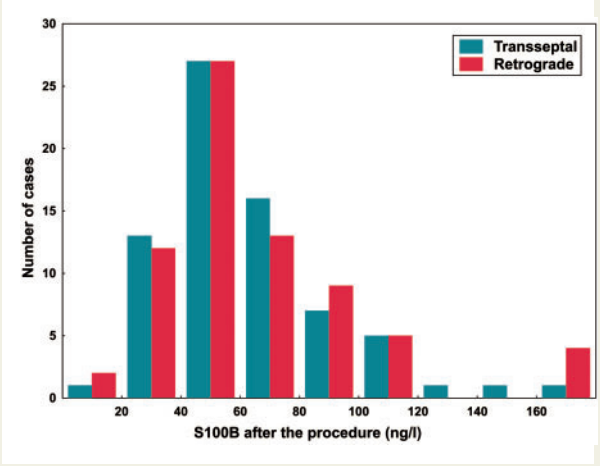

Figure 1 Histogram of absolute levels of S100B after the procedure.

Statistical analysis

Continuous variables were expressed as means with standard deviations and compared with *t*-test for independent samples or Mann–Whitney *U* test or Wilcoxon paired test, as appropriate. Categorical variables were expressed as percentages and compared with χ^2 test or Fisher's exact test. Factors associated with outcome measure ($P < 0.20$) were entered into a multivariate linear regression model and investigated by a stepwise forward method. A *P*-value <0.05 was considered significant. All analyses were performed using the STATISTICA version 10 software (Statsoft, Inc., Tulsa, USA).

Results

Altogether 144 patients were enrolled and randomly allocated into two study groups (72 in each group). Baseline characteristics and procedural data are shown in *Table 1*. Both groups were comparable in baseline characteristics except for the history of a previous cerebral ischaemic event that was more common in transseptal LV access group. In addition, patients in the retrograde LV access group required more intravenous heparin to achieve target ACT levels.

Level of S100B biomarker at baseline was comparable (67 ± 39 vs. 73 ± 50 ng/L, $P = 0.40$) in retrograde vs. transseptal LV access group. It non-significantly increased in patients with retrograde LV access (from 67 ± 39 to 75 ± 77 ng/L, $P = 0.20$) and decreased in patients with transseptal LV access (from 73 ± 50 to 63 ± 29 ng/L, $P = 0.16$). Post-procedure level of S100B for both study groups are displayed in

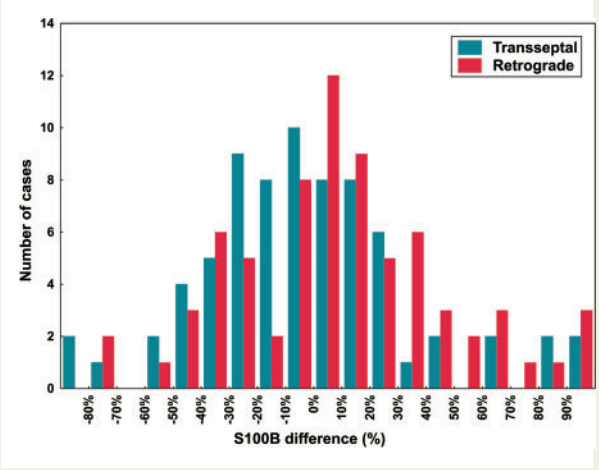

Figure 2 Histogram of relative change of S100B after the procedure.

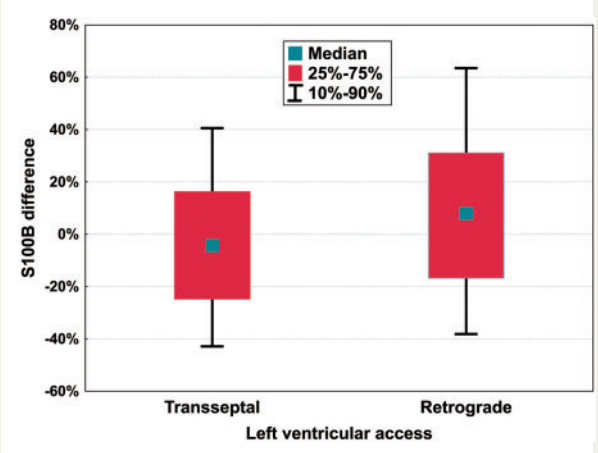

Figure 3 Box–whisker plot of relative change of S100B after the procedure.

Figure 1. Between-group differences in procedure-related change of S100B level were borderline non-significant: 8 ± 67 vs. −10 ± 48 ng/L ($P = 0.053$) in absolute units and 16 ± 73% vs. 0 ± 44% ($P = 0.052$) relatively for retrograde vs. transseptal LV access, respectively (*Figures 2 and 3*). The significant ABI defined as a post-ablation relative increase of S100B level >30% was found in 19.4% of patients. This was observed more often in patients from retrograde vs. transseptal LV access group: 19/72 (26.4%) vs. 9/72 (12.5%), $P = 0.04$. No symptomatic neurological events were noted during and after the procedure in any subject.

The results of linear regression analysis are shown in *Table 2*. Univariately, only retrograde LV access was associated with significant ABI. The association was borderline ($P < 0.20$) for four other factors: age, body mass index, LV ejection fraction, and procedure time. In multivariate analysis, only two factors were independently associated with significant ABI. Patients with retrograde LV access had the rate of significant ABI higher by absolute 15 ± 6% ($P = 0.03$) compared with patients with transseptal LV access. Each decade of age increased the rate of significant ABI by absolute 8 ± 4% ($P = 0.046$).

Table 2 Predictors of significant ABI by linear regression analysis

	Univariate			Multivariate		
	Coeff	SE	*P*-Value	Coeff	SE	*P*-value
Age (years)	0.71	0.38	0.06	0.75	0.38	0.046
BMI (kg/m^2)	−1.2	0.7	0.08			
LVEF (%)	0.57	0.39	0.15			
Retrograde LV access (1/0)	13.9	6.5	0.04	14.6	6.5	0.03
Procedure time (min)	0.103	0.072	0.16			

Table shows only factors that were univariately associated ($P < 0.20$) with significant ABI.
ABI, asymptomatic brain injury; BMI, body mass index; Coeff = slope of regression line between individual factor (unit specified) and the rate of significant ABI (in percentages); LVEF, left ventricular ejection fraction; LV, left ventricle; SE, standard error of coefficient.

Acute efficacy of the procedure

In 24/144 (17%) procedures (12 in each study group), the final programmed ventricular stimulation was not performed due to initial VT non-inducibility. Programmed ventricular stimulation was applicable in 120 of the procedures, of which non-inducibility of any VT was achieved in 77 procedures (64%); 40/60 (67%) and 37/60 (62%) in the retrograde and transseptal group, respectively ($P = 0.57$). The acute outcome was not related to S100B change.

Periprocedural complications

The overall rate of complications was 6.3% without the difference between the retrograde vs. transseptal LV access (6.9% vs. 5.5%). One patient in each group presented with cardiac tamponade. One patient in the transseptal LV access group had acute haemodynamic decompensation with the need for inotropic support. There were two pseudoaneurysms in the retrograde group and none in the transseptal group. There were three local haematomas with a drop of haemoglobin >20 g/L; two in transseptal and one in retrograde LV access group.

Discussion

This randomized clinical trial compared two access routes with the LV during endocardial VT ablation in patients with SHD. Subclinical periprocedural brain damage as assessed by the S100B biomarker was the outcome measure. The main findings can be summarized as follows: (i) significant ABI after LV endocardial ablation can be detected in one-fifth of patients and (ii) retrograde access to LV is associated with a two-fold higher probability of significant ABI.

Because of the study design and the main objective, only a subset of VT patients was investigated excluding those with VT targeted in right ventricle only and those with restricted route to LV substrate either because of mechanical valves or preferential access like in case of LV outflow tract tachycardias. Patients scheduled for pericardial access were also excluded because: (i) epicardial ablation alone has low embolic potential but may be associated with local neural lesions resulting in S100B elevation[8]; (ii) concomitant endocardial ablation, if necessary, is usually performed in a retrograde fashion; and (iii) general anaesthesia is used for all patients with planned epicardial ablation unlike all other patients in our cohort. None of enrolled patients was converted to epicardial ablation during the study procedure.

Brain injury biomarker

The protein S100B is a relatively small protein that belongs to the family of calcium-binding proteins. It is found predominantly found in mature astrocytes, but it may be present in other nervous cells. Its escalated blood levels suggest a neurological dysfunction and cell death. It is released within 24 h after brain injury and its levels correlate with magnitude of neurological deficit and brain injury in stroke.[9] Serial S100B testing has been used for monitoring during various cardiovascular interventions such as carotid endarterectomy,[10] carotid stenting[11] or TAVI.[12] In our previous study, we evaluated correlation between serum S100B levels and cerebral lesions by MRI.[6]

Risk of periprocedural brain injury

Subclinical cerebral microembolism is reported frequently after cardiac interventional procedures. Coronary angiography has shown the incidence of 10–15% ischaemic events after procedure,[13] and in diagnostic aortic valve procedures[14] the number raised to 22%. Transcatheter aortic valve replacement could be associated with up to 84% occurrence of new brain embolic lesions.[15]

In patients undergoing catheter ablation of atrial fibrillation, the reported rate of ABI ranges between 1.7% and 67%, depending on diagnostic criteria, ablation strategy and diagnostic modality.[3,5,16,17] Despite relatively high incidence of ABI, most of the lesions resolve.[4] There is no evidence that neurological deficit could evolve during 6–12 months of follow up.[18] On the other hand, some studies have demonstrated that even asymptomatic lesions may have adverse neurocognitive effects.[19,20]

The rate of ABI and corresponding risk factors in a patient undergoing VT ablation has been much less studied. In a study by Whitman *et al.*,[7] catheter ablation of VT (left-sided procedure) was associated with detectable ABI by MRI in 7/12 (58%) patients. This is substantially higher rate than that in our study (overall 19.4%) and the difference is more striking as our patients had mostly advanced heart disease with low LV ejection fraction and more ablation lesions were delivered. Obviously, methods for ABI detection in both studies are clearly not comparable. The major procedural differences between both studies were retrograde LV access in 92% of patients in a study by Whitman *et al.*, longer procedure time (351 ± 58 vs. 185 ± 46 min) and usage of general anaesthesia. Whether these additional factors could impact the ABI should be investigated in future studies.

The same applies to selecting the optimum ACT level. Anticoagulation was slightly more intensive in transseptal access group, but we did not observe a significant association between both mean and minimum ACT during the procedure and the rate of ABI. However, ACT range as per protocol was rather narrow (300–350 s) which decreased the power to detect any relationship.

Procedural DC shocks may trigger thromboembolic events and contribute to the development of ABI. Direct current shock count did not differ between study groups and was not related to S100B rise. The mean number of shocks was relatively low as most of the induced VTs were terminated by overdrive pacing. In addition, no sustained VT was inducible in substantial proportion of patients (17%) at the beginning of the procedure.

Transseptal vs. retrograde left ventricle access

Multiple mechanisms might be responsible for documented higher rate of ABI associated with retrograde LV access. The cerebral lesions might be attributed to the disruption of either aortic atheroma or debris from the degenerative aortic valves due to multiple attempts to cross the valve. This is relevant to patients with SHD undergoing VT ablation, in whom vascular/valvular disease is common. Irrespective of study findings, preferential use of transseptal LV access facilitates the implementation of the strategy of uninterrupted anticoagulation, which has further potential to reduce the ABI even lower than that demonstrated in this study that enrolled earlier cohorts of patients who all discontinued their oral anticoagulation therapy.

Although retrograde LV access with arterial cannulation may be associated with a higher risk of vascular complications at the puncture site, no significant difference was observed in our study because the overall incidence of vascular complications was very low.

Limitations

The study has several limitations. First, it is a single-centre study that limits the transfer of results into clinical practice. Secondly, detailed neurological evaluation prior/after the ablation procedure was not a part of the study design and we did not verify the raise of S100B by MRI which is considered the gold standard for neural lesion detection. However, no patient showed neurological deficit after the procedure and the majority of patients had ICD, which constitutes relative contraindication to this imaging modality. Thirdly, rate of 'significant' S100B elevation was much lower than expected based on our previous study in population of patients after ablation for atrial fibrillation so that arbitrary cut-off value of >30% was selected for post hoc analysis. Fourthly, post-ablation sample of S100B was taken in the morning on the next day so that the latency was <24 h in small proportion of afternoon procedures. Finally, direct oral anticoagulants were used only sparsely during the study period. Whether their more frequent use would change the outcome of current study is unclear.

Conclusions

Periprocedural brain injury can be detected in one-fifth of patients with SHD undergoing VT ablation at LV endocardium under conscious sedation. Retrograde compared with transseptal LV access showed a two-fold higher probability of significant brain damage. Further studies are needed to elucidate clinical significance of asymptomatic elevation of the S100B marker.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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