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Safety of transvenous lead extraction according to centre volume: a systematic review and meta-analysis

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Background Transvenous lead extraction (TLE) is a complex invasive procedure and the experience of the operator and the team is a major determinant of procedural outcomes.

Aim Because of very limited data available on minimum procedural volumes to enable training and ongoing competency for TLEs, we performed a meta-analysis aimed at assessing the outcomes of TLE in the centres with low, medium, and high volume of procedures.

Methods Of the 280 papers initially retrieved until February 2013, 66 observational studies met inclusion criteria and were included in at least one stratified meta-analysis: 17 were prospective studies; 47 had a retrospective design; and 2 were defined 'experience studies'. We included only articles published after the introduction of laser technique (year 1999). We divided the studies in low, medium, and high volume centres utilizing either the European Heart Rhythm Association (EHRA) or Lexicon classification criteria.

Results When meta-analyses were carried out separately for the studies with larger and smaller sample sizes, either using EHRA or Lexicon classification criteria, no clear differences emerged in the combined rate of major complications or intraoperative deaths. In contrast, both minor complications and mortality at 30 days decreased as centre volume increased.

Conclusions In our meta-analysis of observational studies, patients who have been treated in higher volume centres have a lower probability of minor complications and death at 30 days regardless of the infection rate, length of lead duration, type of device, and type of extraction.

Keywords Transvenous lead extraction • Cardiac device infection • Cardiac device malfunction • Cardiac endocarditis • Centre volume

Introduction

Due to improving recognition of clinical need and wider indications, the implant rate of cardiovascular implantable electronic devices continues to rise in most countries.[1–6] The number of leads per patient is increasing with cardiac resynchronization therapy–pacemaker/defibrillator, upgrades, and a higher proportion of dual- vs. single-chamber devices.[7,8] More commonly, these devices are being used in more elderly patients with significant comorbidities, and long-term complications are arising. Such an increase in device

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What's new?

- Transvenous lead extraction is a complex invasive procedure and the experience of the operator and the team is a major determinant of procedural success and lower rate of complications.
- This systematic review summarizes the existing evidence on the association between the safety of lead extraction and volume centre size.
- Based upon 66 studies including a total of 18 493 patients, we found that minor procedural complications and 30-day mortality were more frequent in low volume centres compared with medium and high volume centres.
- No difference was found for major complications and deaths related to the extraction procedure, with an incidence generally ranging between 0.8 and 1.3%.
- Until more definite evidence with larger and adequately designed prospective studies will be available, it would be advisable to handle high-risk patients in higher volume centres to optimize procedural success minimizing complications.
- The real challenge in extraction has shifted from the operating room or the electrophysiology laboratory to the patient's bed. Although current extraction feasibility and safety are well established, the overall mortality rate at 30 days remains high.

therapy is being paralleled by an increase in the requirement for system transvenous lead extraction (TLE).[1–5] Currently, two-thirds of all extractions are due to cardiovascular device-related infection (CDRI) (lead endocarditis and local device infection), while one-third are due to lead malfunction including lead recall and advisories, which are recently emerging as a new growing indication for lead extraction. In particular, the incidence of cardiac device-related endocarditis ranges from 20 to 25% of all device-related infections as described in recent studies.[1–5,9]

Transvenous lead extraction is a complex invasive procedure and the experience of the operator and the team is a major determinant of procedural success and lower rate of complications.[1–4] Recently, the European Heart Rhythm Association (EHRA) and the Heart Rhythm Society published two documents regarding the pathways for training and accreditation for the centres performing TLE.[1,4]

Many studies reported data that may be used to estimate the association between TLE minimum procedural volumes and outcomes of care. However, these studies differed in design, characteristics of the patients, length of lead stay, and type of technique, and the results are very difficult to interpret examining single trials. We thus performed a systematic review and meta-analysis to investigate the relationship between the safety of TLE and centre procedure volume. We also systematically reviewed the available evidence on other potential predictors (or confounders) of TLE failure/success.

Methods

Bibliographic search and data extraction

Studies evaluating the efficacy or safety of TLE in patients with CDRI or lead malfunction were initially searched in Medline (until February 2013) using the following search strategies: (i) (lead extraction OR TLE or transvenous lead removal) and (pacemaker infections or implantable defibrillator device infections or coronary sinus lead infections or endocarditis), followed by (ii) (lead extraction or TLE or transvenous lead removal) and malfunction. In both searches, terms were searched as words in title/abstract. Additional searches in Scopus and EMBASE were carried out using the above terms; experts were consulted and bibliographies of relevant articles including reviews and meta-analyses were systematically reviewed. No language restriction was applied. Inclusion criteria were: (i) case–control, cohort, or experimental design; and (ii) enough data provided to compare the risk of complications or death according to the number of patients or leads extracted.

More than one study was extracted from one article if more than one dataset was included in the same report (i.e. sub-studies were generated when different populations were analysed in the same study).

Each included article was independently evaluated by two reviewers (ADM, LB), who extracted the main study characteristics and relevant outcome rates (in terms of absolute numbers of events, or all data available to derive such data). In case of ambiguous information on discrepancies in the data extracted by the two reviewers, a third author was contacted (MLN) and consensus achieved through discussion.

We decided a priori not to use a formal quality scoring, but rather to examine the potential influence on overall estimates of single-study characteristics including design, level of statistical adjustment, type of setting, sample size, and outcome definition.

Outcomes and data analysis

The main aim of the analysis was to evaluate the potential relationship between the centre volume and the three primary outcomes of short- and long-term safety: the rate of (i) major complications (cardiac avulsion or tear requiring thoracotomy, pericardiocentesis, chest tube or surgical repair; vascular avulsion or tear requiring thoracotomy, pericardiocentesis, chest tube or surgical repair; pulmonary embolism requiring surgical intervention; respiratory arrest or anesthesia-related complication leading to prolongation of hospitalization; stroke; pacing system-related infection of a previously non-infected site) or deaths within 48 h after lead extraction; (ii) minor complications (including pericardial effusion not requiring pericardiocentesis or surgical intervention; hemothorax not requiring drainage; hematoma at the surgical site requiring reoperation for drainage; arm swelling or thrombosis of implant veins resulting in medical intervention; vascular repair near the implant site or venous entry site; haemodynamically significant air embolism; migrated lead fragment without sequelae; blood transfusion related to blood loss during surgery; pneumothorax requiring a chest tube; pulmonary embolism not requiring surgical intervention) within 48 h; and (iii) deaths within 30 days.

We included in the meta-analysis only the articles published after the introduction of laser technique for TLE procedures.[10] Since almost all included studies were observational with a single arm, no traditional meta-analysis of head-to-head comparisons was possible. We therefore used meta-analyses of proportions to combine data of single arms and obtain summary estimates of the absolute risk of each safety outcome.[11] Several stratified meta-analyses were made to explore the patterns of risk in sub-groups of patients that may be less or more susceptible to bias (including infection rate, length of lead stay, device and technique type), with particular reference to the potential difference in the risk associated with centre volume. In particular, we divided the technique types for lead extraction into three groups: (i) manual extraction, including both simple traction and the traction with stylets; (ii) mechanical extraction, performed with the dilator sheaths; (iii) extraction performed with laser. We did not exclude the articles showing data on leads with <1 year stay.

In addition to sub-group analyses, we evaluated the independent association between the three primary outcomes and centre volume by

Table 1 European Heart Rhythm Association and Lexicon criteria for lead extractor centres

EHRA criteria for lead extractor centres	
Low volume centre	<15 procedures/year
Non-training centre	15–30 procedures/year
Training centre	>30 procedures/year
Lexicon study criteria for extractor centres	
Low volume centre	<60 procedures over 4 years period
Medium volume centre	60–130 procedures over 4 years period
High volume centre	>130 procedures over 4 years period

means of meta-regression analysis, adjusting for multiple potential confounders.[12] Two separate models were fit for each outcome, alternatively including Lexicon[13] or EHRA[4] criteria, based on the number of procedures as indicated in *Table 1* (which could not be included simultaneously due to multicollinearity). In particular, regarding the Lexicon criteria, we should divide the centres into two groups (low volume centre: <15 procedures/year; medium volume centre: 15–30 procedures/year; high volume centre: >30 procedures/year) resulting in the same classification of the EHRA criteria; for this reason, we decided to classify the centres into three groups considering only the absolute values of Lexicon criteria (low volume centre: <60 procedures; medium volume centre: 60–130 procedures; high volume centre: >130 procedures). A stepwise forward technique was used for covariate selection, and only those variables that were significant at a 0.05 level were kept into final models, with the exception of centre volume variables (Lexicon and EHRA criteria), which were forced to entry. Covariates were tested for inclusion either into a continuous form or dichotomized or log-transformed (when skewed according to Shapiro–Wilk test). Since no difference in significance was noted with transformed or dichotomized covariates, all were maintained in their original form. In order to reduce potential overfitting and false-positive results, the number of variables included in both final and intermediate models (during modeling) was limited to four to six depending on the number of studies available for each outcome. Final models were also checked for potential multicollinearity and interactions.

The assessment of the potential publication bias was problematic, both because of the outcome nature (rates with the lower confidence limit inevitably trimmed to zero) and because in this specific context differences according to the study sample size may have valid explanations alternative to publication bias. In other terms, the scenario typically suggestive of publication bias—a better (lower) summary estimate of an outcome (i.e. major complications) in smaller- vs. larger-sample studies—was difficult to interpret and attribute to publication bias rather than to a difference in the safety due to the centre procedure volume, which was in fact the major aim of the meta-analysis. In any case, funnel plots displaying the outcome rate from individual studies vs. their precision (1/standard error)[14] were carried out with an exploratory aim.

We used StatsDirect 2.7.9 (StatsDirect Ltd, 2012) and Stata 11.1 (Stata Corp., College Station, 2009) to perform proportion meta-analyses and meta-regression, respectively.

Results

Of the 280 papers initially retrieved (*Figure 1*), 66 observational studies met inclusion criteria and were included in at least one

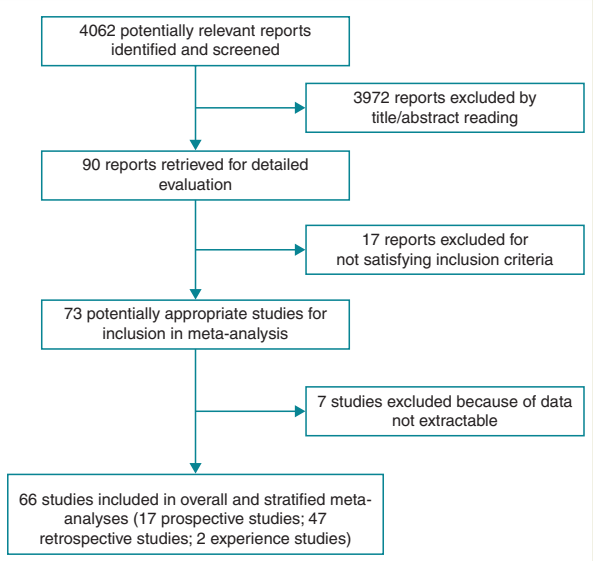

Figure 1 Flow of the included studies in each stage of the bibliographic search.

stratified meta-analysis: 17 were prospective studies;[10,15–27] 47 had a retrospective design;[13,28–69] and 2 were defined 'experience studies'.[70,71] The main characteristics of these studies are available in *Table 2*: most studies were published after 2005 and were performed in Western countries (29 in USA; 9 in UK; 8 in Italy; 5 in Canada and France; 5 in Sweden; 2 in Germany, the Netherlands, Belgium, Turkey; 1 in Austria, Argentina, Switzerland, Portugal, Denmark, Poland, Lebanon, and China). The 17 prospective studies evaluated a total of 4690 patients, while the 47 retrospective studies included 13 548 subjects; and the two experience studies enrolled 195 patients. We also retrieved two randomized controlled trials which, however, were not included in the analyses with observational studies.[72,73] The analysis concentrated on the centres volume and their available data while no individual operator data could be obtained.

Overall efficacy and safety

In 66 observational studies, including a total of 18 433 subjects, 303 major complications or deaths were recorded within 48 h after lead removal, corresponding to a crude rate of 1.6% (95% confidence Interval—CI: 1.5–1.8%—*Table 3*). The overall rate estimated through proportion meta-analysis was slightly higher: 1.8% (1.4–2.2%).

All but one observational study also recorded the incidence of minor complications within 48 h after lead extraction, reporting a total of 431 events, corresponding to crude and combined rates, respectively, of 2.4% (2.2–2.6%) and 3.0% (2.2–2.4%—*Table 3*).

Only 22 observational studies—including a total of 9783 subjects—evaluated the third primary outcome: mortality within 30 days from extraction. The main reasons of death at 30 days were sepsis and endocarditis. Again, the raw mortality was slightly lower than the one estimated using proportion meta-analysis: 1.5% (1.3–1.8%) vs. 1.8% (1.1–2.6%), respectively (*Table 3*).

Table 2 Characteristics of published studies investigating the safety of lead extraction

First Author (Ref.)	Study year	Country	Design[a]	Multi-centric	Centre volume	EHRA criteria	Lexicon criteria	Mean age, yy	Rate of infections[b]	Number of leads	Lead stay[c]	% of PM	% of ICD	% of CRTP/D	Outcomes extracted[d]
Epstein 1[10]	1999	USA	Prosp.	Yes	863	>30	>130	63.0	56.0	1285	75.0	NA	NA	NA	1,2,3
Kennergren 1[15]	2000	Sweden, USA, Canada	Prosp.	Yes	57	>30	<60	67.0	NA	99	60.0	91	9	0	1,2
Khantaria[16]	2000	USA	Prosp.	No	42	>30	>130	59.0	45.2	50	13.7	0	100	0	1,2
Byrd[28]	2002	USA	Retros.	Yes	1864	>30	>130	64.0	NA	2561	76.0	NA	NA	NA	1,2,3
Klug[29]	2002	France	Retros.	No	39	>30	60–130	72.0	NA	82	113.0	NA	NA	NA	1,2
Moon[30]	2002	USA	Retros.	No	128	>30	60–130	64.0	53.0	229	61.0	61	39	0	1,2
Cooper[31]	2003	USA	Retros.	No	14	<15	<60	17.9	0.0	21	42.0	19	81	0	1,2
Mathur[32]	2003	UK	Retros.	No	80	<15	60–130	58.5	41.1	165	76.0	97.5	2.5	0	1,2,3
Meyer-Ewert[33]	2003	USA	Retros.	No	9	<15	<60	66.0	100.0	17	NA	76.3	23.7	0	1,2,3
Saad[34]	2003	USA	Retros.	No	161	15–30	>130	61.0	46.6	161	31.8	0	100	0	1,2
Burke[17]	2005	USA	Prosp.	No	28	15–30	<60	73.0	40.0	55	10.2	NA	NA	18	1,2
Kasravi[35]	2005	USA	Retros.	No	149	<15	>130	71.5	NA	14	17.0	0	0	100	1,2
Guynor[36]	2006	USA	Retros.	No	283	>30	>130	64.0	59.0	500	NA	67	33	0	1,2
Ruttmann[37]	2006	Austria	Retros.	No	30	<15	<60	66.6	100.0	43	22.7	89.6	10.4	0	1,2
Bongiorni 1[18]	2007	Italy	Prosp.	No	37	<15	<60	68.1	72.7	37	19.5	0	0	100	1,2
Kennergren 2[38]	2007	Sweden, UK, Germany, Switzerland, The Netherlands, Portugal, Denmark, Belgium	Retros.	Yes	292	>30	>130	61.6	39.8	383	74.0	87	13	0	1,2,3
Khairy 1[19]	2007	Canada	Prosp.	No	159	>30	>130	63.7	44.0	288	92.4	80.5	19	0.5	1,2
Khairy 2[19]	2007	Canada	Prosp.	No	16	>30	>130	43.0	44.0	23	108.0	87	13	0	1,2
Roux[20]	2007	Canada	Prosp.	No	175	>30	>130	62.0	49.7	270	93.6	80	19.5	0.5	1,2
Bongiorni 2[21]	2008	Italy	Prosp.	No	1193	>30	>130	65.7	83.5	2065	69.3	85	11	4	1,2
Gula[39]	2008	UK	Retros.	No	154	>30	>130	64.5	74.0	278	91.2	69.5	30.5	0	1,2,3
Jones[40]	2008	USA	Retros.	No	498	>30	>130	63.2	88.5	975	90.0	52.2	45.3	2.5	1,2
Agarwal[41]	2009	USA	Retros.	No	212	>30	>130	65.0	78.2	465	67.0	51	49	0	1,2,3
Calvagna[42]	2009	Italy	Retros.	No	300	>30	>130	67.0	74.0	518	86.0	78	11	11	1,2
Hamid 1[22]	2009	UK	Prosp.	No	265	>30	>130	67.0	56.2	97	26.5	49.5	17.5	33	1,2
Kennergren 3[43]	2009	Sweden	Retros.	No	592	>30	>130	62.8	59.0	1032	69.0	94	5.5	0.5	1,2,3
Kutarski[44]	2009	Poland	Retros.	No	120	>30	60–130	65.7	74.2	236	82.7	NA	NA	NA	1,2
Marijon[45]	2009	France	Retros.	Yes	311	>30	>130	70.0	67.5	590	85.2	90.2	5.9	3.9	1,2,3
Scott 1[46]	2009	UK	Retros.	No	31	<15	60–130	65.0	77.0	60	80.4	85	11.6	3.4	1,2
Scott 2[46]	2009	UK	Retros.	No	43	<15	60–130	65.0	77.0	80	105.6	78	11	11	1,2
Bordachar 1[23]	2010	France	Prosp.	Yes	356	>30	>130	70.0	82.2	746	10.0	83	17	0	1,3
Bordachar 2[23]	2010	France	Prosp.	No	101	>30	60–130	71.0	88.5	222	12.0	88	12	0	1,2,3

Continued

Table 2 *Continued*

First Author (Ref.)	Study year	Country	Design[a]	Multi-centric	Centre volume	EHRA criteria	Lexicon criteria	Mean age, yy	Rate of infections[b]	Number of leads	Lead stay[c]	% of PM	% of ICD	% of CRTP/D	Outcomes extracted[d]
Cecchin[47]	2010	USA	Retros.	No	144	15–30	>130	14.9	8.0	203	72.4	80	19	1	1,2
Grammes[48]	2010	USA	Retros.	No	100	>30	>130	67.0	100.0	1838	50.9	NA	NA	NA	1,2
Hamid 2[70]	2010	UK	Exper.	No	183	>30	>130	65.0	59.0	369	75.0	73	17	10	1,2,3
Hussein[49]	2010	USA, Lebanon	Retros.	No	29	15–30	<60	64.4	69.0	41	111.0	52	48	0	1,2
Kratz[50]	2010	USA	Retros.	No	365	15–30	>130	62.0	64.4	365	NA	75	25	0	1,2
Maytin 1[51]	2010	USA, Italy	Retros.	Yes	348	>30	>130	59.9	22.8	349	27.0	0	100	0	1,2,3
Rusanov[52]	2010	USA	Retros.	No	79	<15	60–130	57.5	73.4	152	56.2	87.5	11.2	1.3	1,2
Wazni[13]	2010	USA, Canada	Retros.	Yes	1448	>30	>130	63.4	56.9	2405	82.1	NA	NA	NA	1,2
Henrikson[53]	2011	USA	Retros.	No	67	15–30	60–130	69.0	100.0	NA	76.0	69	25	6	1,2,3
Franceschi[24]	2011	France, Canada	Prosp.	Yes	684	>30	>130	65.0	66.2	1364	72.0	78	15	7	1,2
Maytin 2[54]	2011	USA	Retros.	No	139	<15	>130	64.0	51.0	239	13.2	33.7	49.6	16.7	1,2
Rodriguez 1[55]	2011	USA	Retros.	No	388	>30	>130	64.2	76.0	814	38.6	36	47	17	1,2
Rodriguez 2[55]	2011	USA	Retros.	No	188	>30	>130	85.0	84.0	253	59.6	56	28	16	1,2
Williams 1[56]	2011	UK	Retros.	No	71	<15	60–130	71.0	62.0	203	35.8	0	0	100	1,2,3
Aksu[71]	2012	Turkey	Exper.	No	12	<15	<60	58.0	75.0	14	73.0	71	29	0	1,2
Ali Oto[57]	2012	Turkey	Retros.	No	66	15–30	60–130	55.6	59.1	140	85.0	42.3	39.4	18.3	1,2
Arujuna[58]	2012	UK	Retros.	No	386	>30	>130	65.5	66.8	745	85.4	55.7	25.6	18.7	1,2,3
Chu[59]	2012	China	Retros.	No	23	<15	<60	63.8	66.7	24	29.5	0	0	100	1,2,3
Da Costa[25]	2012	France	Prosp.	No	49	>30	>130	66.0	0.4	125	NA	34.4	39.2	26.4	1,2
Di Cori[26]	2012	Italy	Prosp.	No	145	<15	>130	61.0	80.0	147	29.0	0	0	100	1,2,3
Geselle[60]	2012	Belgium	Retros.	No	157	15–30	>130	69.0	18.0	259	58.0	NA	NA	NA	1,2
Maytin 3[61]	2012	USA	Retros.	No	985	>30	>130	63.4	50.0	1951	70.8	38	51	11	1,2
Maytin 4[62]	2012	USA, Italy, Sweden	Retros.	Yes	12	>30	<60	62.0	67.0	12	14.2	0	0	100	1,2,3
Pelargonio 1[27]	2012	Italy, USA	Prosp.	Yes	652	>30	>130	71.0	94.0	1410	29.0	NA	NA	NA	1,2
Pelargonio 2[27]	2012	Italy, USA	Prosp.	Yes	150	>30	>130	65.0	94.0	301	42.0	NA	NA	NA	1,2
Perez Baztarrica 1[63]	2012	Argentina	Retros.	No	8	<15	<60	65.0	100.0	14	12.5	88	12	0	1,2
Perez Baztarrica 2[63]	2012	Argentina	Retros.	No	13	<15	<60	65.0	100.0	23	12.5	85	15	0	1,2
Rickard[64]	2012	USA	Retros.	No	173	15–30	>130	84.0	100.0	173	22.3	0	0	100	1,2
Sheldon[65]	2012	USA	Retros.	No	115	<15	60–130	68.7	49.0	125	18.5	0	0	100	1,2
Williams 2[66]	2012	UK	Retros.	No	334	>30	>130	67.2	62.0	657	74.2	72.3	19	8.7	1,2
Williams 3[66]	2012	UK	Retros.	No	72	>30	>130	62.0	79.8	141	70.6	75.1	14.8	10.1	1,2,3
de Bie[67]	2012	The Netherlands	Retros.	No	279	15–30	>130	84.0	58.4	445	50.4	36.8	32.3	30.9	1,2,3
Epstein 2[68]	2013	USA, Italy, Sweden	Retros.	Yes	2201	>30	>130	61.0	86.8	2274	43.0	0	100	0	1,2,3
Lisy[69]	2013	Germany	Retros.	No	41	15–30	<60	64.0	22.0	78	31.0	0	0	100	1,2

NA, not available.
[a]Prosp., prospective study; Retros., retrospective study; Exper., experience study.
[b]Percentage of local + systemic infections.
[c]Length of lead stay, in months.
[d]1, major complications (see the text); 2, minor complications (see the text); 3, deaths within 30 days after lead extraction.

Table 3 Absolute percentages of subjects with major or minor complications after lead extraction, according to several variables including centre volume

	Major complications + procedural death[a]			Minor complications[b]			30-day mortality		
	% (95% CI)	No of studies (no. of patients)	(Ref.)	% (95% CI)	No of studies (no. of patients)	(Ref.)	% (95% CI)	No of studies (no. of patients)	(Ref.)
All studies—crude rate[c]	1.6 (1.5–1.8)	66 (18 433)	10,13,15–71	2.4 (2.2–2.6)	65 (18 077)	10,13,15–71	1.5 (1.3–1.8)	22 (9783)	10,23,28,32,33,38,39,41,43,45,51,53,56,58,59,61,66,67,70
All studies—combined rate	1.8 (1.4–2.2)	66 (18 433)		3.0 (2.2–4.0)	65 (18 077)		1.8 (1.1–2.6)	22 (9783)	
EHRA (*n* patients per year)									
<15	1.8 (0.7–3.6)	17 (1005)	18,26,31–33,35,37,46,52,54,56,59,63,65,71	7.2 (4.1–11.2)	17 (1005)	18,26,31–33,35,37,46,52,54,56,59,63,65,71	5.3 (1.3–11.7)	4 (183)	32,33,56,59
15–30	2.0 (1.3–2.7)	11 (1510)	17,34,47,49,50,53,57,60,64,67,69	3.1 (1.2–6.0)	11 (1510)	17,34,47,49,50,53,57,60,64,67,69	3.0 (1.0–21.0)	2 (346)	53,67
>30	1.8 (1.3–2.3)	38 (15 918)	10,13,15,16,19–25,27–30,36,38–45,48,51,55,58,61,62,66,68,70	2.1 (1.3–3.1)	37 (15 562)	10,13,15,16,19–25,27–30,36,38–45,48,51,55,58,61,62,66,68,70	1.5 (0.9–2.3)	16 (9254)	10,23,28,38,39,41,43,45,51,58,61,66,70
Lexicon (*n* patients overall)									
<60	2.0 (0.3–5.2)	13 (320)	15,17,18,31,33,37,49,59,62,63,69,71	8.5 (3.6–15.1)	13 (320)	15,17,18,31,33,37,49,59,62,63,69,71	14.6 (4.9–28.2)	2 (32)	33,59
60–130	2.8 (1.8–4.1)	12 (940)	23,29,30,32,44,46,52,53,56,57,65	3.4 (1.3–6.5)	12 (940)	23,29,30,32,44,46,52,53,56,57,65	3.6 (0.9–8.0)	4 (319)	23,32,53,56
>130	1.6 (1.2–2.1)	41 (17 173)	10,13,16,19–22,24–28,34,36,38–43,45,47,48,50,51,54,55,58,60,61,64,66–68,70	2.3 (1.5–3.4)	40 (16 817)	10,13,16,19–22,24–28,34,36,38–43,45,47,48,50,51,54,55,58,60,61,64,66,67,68,70	1.4 (0.8–2.2)	16 (9432)	10,28,38,39,41,43,45,51,58,61,66,67,70
Publication year									
<2010	2.3 (1.5–3.3)	30 (8145)	10,15–22,28–46	2.8 (1.6–4.3)	30 (8145)	10,15–22,28–46	1.5 (0.7–2.7)	9 (4377)	10,28,32,33,38,39,41,43,45
≥2010	1.4 (1.0–1.7)	36 (10 288)	13,23–27,47–71	3.2 (2.0–4.5)	35 (9932)	13,23–27,47–71	2.1 (1.1–3.5)	13 (5406)	23,51,53,56,58,59,61,66,67
Local + systemic infection									
<60%	1.9 (1.2–2.8)	26 (7052)	10,13,16,17,19,20,21,25,30–32,34,36,38,43,47,51,54,57,61,65,67,69,70	3.1 (1.8–4.6)	26 (7052)	10,13,16,17,19,20,22,25,30–32,34,36,38,43,47,51,54,57,60,61,65,67,69,70	0.9 (0.3–1.8)	8 (2759)	10,32,38,43,51,61,67,70

Continued

Table 3 *Continued*

	Major complications + procedural death[a]			Minor complications[b]			30-day mortality		
	% (95% CI)	No of studies (no. of patients)	(Ref.)	% (95% CI)	No of studies (no. of patients)	(Ref.)	% (95% CI)	No of studies (no. of patients)	(Ref.)
≥60%	1.7 (1.2–2.2)	36 (9272)	18,21,23,24,26,27,33,37, 39–42,44–46,48–50,52,53, 55,56,58,59,62–64,66,68,71	3.5 (2.1–5.2)	35 (8916)	18,21,23,24,26,27,33,37, 39–42,44–46,48–50, 52,53,55,56,58,59, 62–64,66,68,71	3.0 (1.5–5.0)	12 (2094)	23,33,39,41,45,53,56,58,59,66
Lead stay									
<60 months	1.1 (0.8–1.5)	30 (6472)	16–18,22,23,26,27,31,34, 35,37,48,51,52, 54–56,59,60,62–65,67–69	4.0 (2.4–6.0)	29 (6116)	16–18,22,23,26,27, 31,34,35,37,48,51,52, 54–56,59,60,62–65,67–69	1.6 (0.5–3.3)	6 (3379)	23,51,56,59,67
≥60 months	2.0 (1.5–2.6)	32 (11 255)	10,13,15,19–21,24,28–30, 32,38–47,49,53,57,58,61, 66,70,71	2.4 (1.4–3.6)	32 (11 255)	10,13,15,19–21,24,28–30,32, 38–47,49,53,57,58,61, 66,70,71	1.9 (1.1–2.8)	13 (6395)	10,28,32,38,39,41,43,45, 53,58,61,66,70
Type of device									
>50% of Pacemaker	1.8 (1.3–2.3)	31 (6627)	15,19–21,24,30,32,36–43, 45–47,49,50,52,53,55, 58,63,66,70,71	3.7 (2.6–5.0)	31 (6627)	15,19–21,24,30,32,36–43, 45–47,49,50,52,53,55,58, 63,66,70,71	1.5 (0.6–2.8)	10 (2568)	32,38,39,41,43,45,53,58,66,70
>50% of ICD	1.1 (0.3–2.4)	6 (2978)	16,31,34,51,61,68	3.3 (0.4–8.7)	6 (2978)	16,31,34,51,61,68	1.1 (0.05–3.5)	2 (1303)	51,61
>50% of CRT	1.3 (0.5–2.4)	9 (766)	18,26,35,56,59,62,64,65,69	6.8 (4.0–10.4)	9 (766)	18,26,35,56,59,62,64,65,69	13.0 (3.0–34.0)	2 (94)	56,59
Type of extraction									
>50% manual	1.6 (1.1–2.1)	36 (11 362)	10,13,15–18,20,22,24,26,28, 30,34–39,49,52,54–57,59, 60,63–68,70	2.7 (1.7–3.8)	36 (11 362)	10,13,15–18,20,22,24,26,28, 30,34–39,49,52,54–57, 59,60,63–68,70	1.1 (0.5–2.0)	10 (6650)	10,28,38,39,56,59,66,67,70
>50% mechanical	0.9 (0.6–1.2)	13 (4790)	21,25,32,34,42,43,49, 52,57,63,68,71	5.6 (2.3–10.2)	13 (4790)	21,25,32,34,42,43,49,52, 57,63,68,71	0.4 (0.2–0.6)	3 (2873)	32,43,68
>50% laser	2.0 (1.5–2.6)	26 (12 105)	10,13,19,20,23,27,28,31, 34,38–41,43,46,47,50,55, 61,62,66,68	2.1 (1.2–3.2)	25 (11 749)	10,13,19,20,23,27,28,31, 34,38–41,43,46,47,50,55, 61,62,66,68	1.2 (0.6–1.9)	11 (7692)	10,23,28,38,39,41,43,61,66

Data from single studies have been combined using proportion meta-analysis (random-effects model).
N, total number of subjects analyzed; (ref), references to included studies; CI, confidence intervals.
[a]Major complications (see the text).
[b]Minor complications (see the text).
[c]The simple rate between the number of events and the sample size, while the combined rate is the summary estimate of the random-effects proportion meta-analysis.

Table 4 Results of multiple meta-regression analyses relating centre volume and other variables to effect size estimates of studies evaluating the rate of each of the primary outcomes of efficacy of lead extraction

Variables included in the model[a]	Regression coefficient	*P*		Regression coefficient	*P*
Model 1					
Major complications + death[b]					
EHRA (*n.* patients per year)			Lexicon (*n.* patients overall)		
<15 (Ref. cat.)	0	–	<60 (Ref. cat.)	0	—
15–30	−0.153	0.8	60–130	−3.331	0.3
>30	0.686	0.2	>130	−3.344	0.2
Length of lead stay, 1-month increase	0.021	0.002			
Model 2					
Minor complications[c]					
EHRA (*n.* patients per year)			Lexicon (*n.* patients overall)		
<15 (Ref. cat.)	0	—	<60 (Ref. cat.)	0	—
15–30	−6.107	0.027	60–130	−6.396	0.031
>30	−6.792	0.003	>130	−6.861	0.005
% of mechanical extractions, one-point increase	0.056	0.035			
Model 3					
30-day mortality					
EHRA (*n.* patients per year)			Lexicon (*n.* patients overall)		
<15 (Ref. cat.)	0	—	<60 (Ref. cat.)	0	—
15–30	−1.831	0.5	60–130	−8.201	0.002
>30	−5.189	0.013	>130	−10.27	<0.001

Except for centre volume, the variables extracted from individual studies that are not showed in the table were not significant in the final multivariate models. See the text for further details on meta-regression modelling.
[a]Two separate models were fit for each outcome, alternatively including Lexicon or EHRA criteria (which could not be included simultaneously due to multicollinearity).
[b]Major complications (see the text).
[c]Minor complications (see the text).

The rates of all above primary outcomes for each individual observational study are available in the online supplementary forest plots (Supplementary material online, *Figures S1–S3*).

The first randomized trial[72] was carried out on 60 patients (161 leads overall), and reported zero deaths, two major and one minor complications. The second randomized trial[73] was carried out on 301 patients (465 leads overall), and reported one death and eight major complications.

Meta-analyses stratified by centre volume

As we had only two randomized trial,[72,73] stratified meta-analyses could be made only for observational studies. When meta-analyses were carried out separately for the studies with larger and smaller sample sizes, either using EHRA or Lexicon classification criteria, no clear differences emerged in the combined rate of major complications or deaths (*Table 3*). In contrast, both minor complications and mortality at 30 days decreased as centre volume increased.

In particular, the combined rate of minor complications from the 17 studies with less than 15 patients per year, or from the 13 studies with less than 60 patients overall, was as high as 7.2 or 8.5%, respectively, while the same rates from the studies with more than 30 patients per year, or more than 130 patients globally, were 2.1 and 2.3%, respectively (both *P*-values <0.001). Although fewer studies were available, thus significance was not achieved in univariate analysis, the same trend was observed for 30-day mortality: the rate of deaths was 5.3 or 14.6% pooling lower volume studies according to EHRA or Lexicon criteria, respectively, and 1.5 or 1.4% combining higher volume studies.

Importantly, the results of the stratified meta-analyses were entirely confirmed by multiple meta-regression (*Table 4*). The strong, inverse association between centre volume and both 30-day mortality and minor complications remained highly significant even after adjusting for several potential confounders such as infection rate, length of lead duration, publication year, study design, type of device, and type of extraction.

Meta-analyses stratified by other variables

Despite some relevant differences in stratified proportion meta-analyses, as indicated in *Table 3*, once centre volume was adjusted for in multiple meta-regression neither the publication year, nor the rate of systemic or local infections or the type of device were associated with significant variations in the summary estimate of risk for any of the outcomes (*Table 4*). Also, in proportion meta-analyses as well as in meta-regression, only marginal and not

significant differences in summary estimates of 30-day mortality were observed according to the type of extraction and the length of lead stay. In contrast, the studies with a mean lead indwelling time >60 months showed higher rates of major complications in proportion meta-analyses, and lead duration (treated continuously) was significantly associated with an increased risk of major complications even after multiple adjustments ($P = 0.002$—*Table 4*). A higher summary rate of minor complications was observed combining the studies with most mechanical extractions (*Table 3*), and such a difference was confirmed in meta-regression after controlling for centre volume and other covariates ($P = 0.0.035$—*Table 4*). Finally, a trend towards a higher risk of major complications was found in this sub-group of patients who underwent TLE with the laser technique (*Table 3*).

Publication bias

Funnel plots displaying each outcome rate for the individual studies vs. the reciprocal of their standard error have been reported in the Supplementary material online, *Figures S4–S6*. All appear skewed to the left, and if they are to be interpreted traditionally, such patterns would suggest that the risk associated with lead extraction might be lower than the current estimates. However, as anticipated, the interpretation of funnel plots is problematic in the present study, as an asymmetric graph may likely be caused by a difference in safety or efficacy due to centre volume. Thus, such graphs have been reported only for exploratory purposes and their interpretation must take into account the specific rationale of the study.

Discussion

Over the past decade, there has been an increase in the number of implanted cardiac devices that has been paralleled by an increase of device extraction. As a consequence, many centres have started performing such procedures, with different results.[10,13–71,74–77] The issue whether the volume of the centre may affect the outcome of the procedure has always been questioned, but no conclusions could be drawn so far. This systematic review summarizes the existing evidence on the association between the safety of TLE and volume centre size.

Based upon 66 studies including a total of 18 493 patients, we found that an acute successful procedure can be achieved regardless of the volume size, either at low or at high volume centres; however, minor procedural complications and 30-day mortality were more frequent in low volume centres compared with medium and high volume centres, either using EHRA or Lexicon criteria. No difference was found for major complications and deaths related to the extraction procedure, with an incidence generally ranging between 0.8 and 1.3%.[13,28–69]

Since new technologies have been supporting the extraction procedures, the success rate has increased in many centres, raising from 80 in the 90s, up to 94% or more nowadays.[3] Although the number of extracted leads is different among volume centre size, and higher volume centres receive more cases as they mostly are referral centres, success is highly achieved regardless of the volume size.[3] All extraction techniques were used in all centres, but laser was extensively used in high volume centres. This has been previously observed by Wazni *et al.*[13] and reflects the higher level of experience and training achieved by higher volume centres compared with the others. Laser may increase the success of the procedure but it might also be responsible for higher risk of complications in non-experience hands,[1,3,4] and our data on this issue are in line with the literature, with a trend towards a higher risk using laser (*Table 3*).

Major findings

Our analysis supports a higher rate of minor complications in lower volume compared with higher ones. This finding is in line with previous reports[3,4,13] where lower volume centres have less experience and more complications. Minor complications may be the consequence of a lower ability in handling less serious problems in lower volume size, meaning probably that the peri-procedural management might be different among centres. A trend towards longer lead age in lower volume centres might be one of the possible confounders to be considered in the different results. The new advances in extraction technologies obtained through these years may have allowed lower volume centres to reduce their major but not minor complications, which are more linked to the operator's experience and training.

The real challenge in extraction has shifted from the operating room or the electrophysiology laboratory to the patient's bed. Although current extraction feasibility and safety are well established, the overall mortality rate at 30 days remains high. Our findings support two concepts: mid-term mortality of extracted patients is higher in low volume centres, but it remains higher also regardless of the volume size of the centre. Particularly, lower volume centres may be less equipped and trained to manage more complex cases and patients at high risk may find less adequate multidisciplinary resources to take care of their co-morbidities and complications in such environments, while more often high volume centres are tertiary referral centres whose ability in high-risk patient management is related to their training and hospital facilities to handle critical cases.

Lead extraction is today an acceptable safe procedure, with an overall estimated mortality risk <1%[3] thanks to the technical and surgical efforts made through these years. But if the first step has been achieved, the goal to impact on the total mortality of patients undergoing lead extractions has not been reached. In hospital and mid-term mortality after lead extraction has been reported to be high mainly in patients with systemic infections or pocket infections, both independent risk factors for reduced survival.[53] In the Lexicon study, there was a 6-fold increase of mortality risk in the presence of renal failure and cardiac infections.[13] Maytin *et al.*[61] described a cumulative 8.4 and 46.8% mortality rate at 1 and 10 years, respectively, after lead extraction and identified serum creatinine, diabetes, increasing age, and systemic infections as predictors of worse outcome. Unfortunately, our analysis was unable to assess mortality risk factors due to lack of data, mainly on clinical features and co-morbidities. However, we observed a non-significant trend towards a higher 30-day mortality rate in carriers of more complex devices, such as CRT devices, older leads, infections (whether local or systemic), and type of extractions (laser vs. other techniques).

Minor findings

Major complications and death related to the procedure are mainly linked to technical issues and to the presence of patients' own risk factors, to device and lead models, to the lead age, and to the ability and the experience of the physicians.[1,3,4] In our study, no

significant difference could be found in the rate of major complications among centres, in contrast to previous data reported by Wazni *et al.*[13] These authors reported a higher number of deaths and complications in low volume centres, claiming the main cause to be the different learning curve. However, the data coming from the literature usually compare the overall complications among centres, without differentiating major from minor complications, thus summing both results in one and supporting an increased number of complications in lower volume ones. Also, although speculative, the lack of different major complication rate might be related to the different centres' learning curve, which is not only affected by the number of extractions performed, but also by the time dedicated to such expertise.

Peri-procedural death was higher in the reports from the early 2000 compared with the last years, and evidence from recent data supports a new range from 0.8 to 1%,[1,3,4] as confirmed in our review. Operator skills, a dedicated team, and the ability to manage complications have all contributed to a decrease in the mortality rate.

Limitations

This meta-analysis has several limitations that must be considered in interpreting the results. First, the classification of centre volume obtained by the ratio between the number of patients and the length of study could not represent the real volume of the centre. Secondly, in the multicentre studies we were not able to calculate the volume of each centre because of the lacking data in the published articles; however, most multicentre studies were performed in high volume centres. Thirdly, several studies are performed by the same groups/centres and it is possible that an outcome (either major or minor complication) could be counted/represented more than once. Fourthly, we used centre volume as a proxy of operator skills; however, we could not know each operator specific experience. Fifthly, as regards stratified proportion meta-analysis to compare the outcome rates of studies with larger or lower centre volume, such analysis has the advantage that it allows the inclusion of data from single-arm studies. However, given that these analyses are only stratified and do not refer to head-to-head comparisons, the results should be interpreted with caution. Sixthly, a few studies had specific populations (with congenital diseases, over 80 years, endocarditis >20 mm). However, exclusion of these studies did not materially change the results (data not shown). Seventhly, although the interpretation of funnel plots was problematic in this particular case, as for any meta-analysis the existence of publication bias cannot be ruled out.[78] Finally, our results on 30-day deaths were based upon a relatively low number of cases ($n = 146$) and should be interpreted with caution.

Conclusion

The results of this meta-analysis show that procedure volume is a major determinant of outcomes of transvenous lead extraction. Until more definite evidence with larger and adequately designed prospective studies will be available, it would be advisable to handle high-risk patients in higher volume centres to optimize procedural success minimizing complications. If a low volume centre encounters a difficult complex case, every effort should be made to keep the leads intact.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

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Sustained ventricular tachycardia and coved-type electrocardiogram in peripheral leads: a particularly malignant phenotype of Brugada syndrome?

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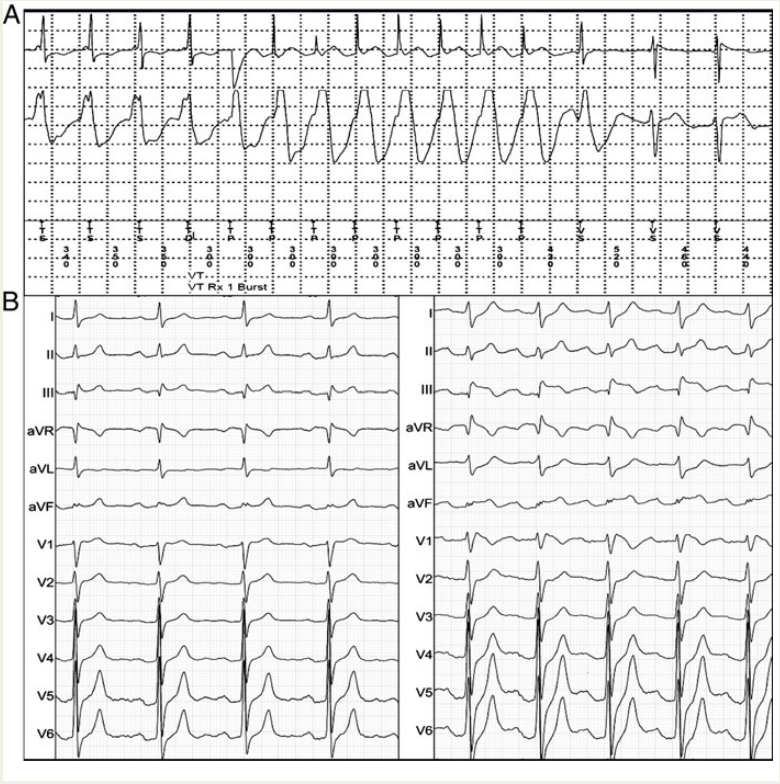
A 64-year-old man was admitted at our hospital for appropriated implantable cardioverter-defibrillator (ICD) interventions. He underwent ICD implantation 7 months before because of ventricular fibrillation (VF) in the absence of structural heart disease.

During the follow-up, he presented both VF and monomorphic ventricular tachycardia (MVT), mostly treated by ICD with efficacious antitachycardia pacing (*Figure A*). In two cases, arrhythmic episodes happened during a febrile episode.

Programmed ventricular stimulation failed to induce any kind of arrhythmia. After administration of intravenous ajmaline (0.5 mg/kg), the electrocardiogram (ECG) showed a Brugada pattern (BP) in V1 and peripheral leads (*Figure B*). The test has been considered diagnostic for Brugada syndrome (BS).

Brugada syndrome is a primarily arrhythmic disorder that predisposes to malignant ventricular arrhythmias, in the absence of gross structural abnormalities. A spontaneous or drug-induced BP in peripheral ECG leads seems to be present in up to 10% of BS population, and it has been associated with a worse prognosis.



Brugada syndrome is typically related to polymorphic ventricular tachycardia. Rarely cases of MVT have been reported.

The peculiarity of this case is the contemporary presence of two rare aspects of the BS: MVT and BP in peripheral leads during ajmaline test. The latter could explain the particularly severe phenotype.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/Malignant-ventricular-arrhythmias.pdf.