Review Article

The Diagnosis and Treatment of Pacemaker-Associated Infection

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Summary

Background: Approximately 105 000 cardiac electronic devices are newly implanted in Germany each year. Germany has the highest implantation rate with respect to population of any European country. Infections in cardiac implants are serious complications, with an associated in-hospital mortality of 5–15%. It is thus very important to optimize the diagnostic and therapeutic strategies by which such infections can be detected early and treated effectively.

Methods: This review is based on pertinent publications retrieved by a search in PubMed, with special attention to the current recommendations of international medical specialty societies.

Results: According to the international literature, the incidence of device-associated infection is 1.7% (in six months) for implanted defibrillators and 9.5% (in two years) for resynchronization devices. No absolute figures on infection rates are available for Germany. Infection can involve either the site where the impulse generator is implanted or the intravascular portion of the electrodes. The most important elements of the diagnostic evaluation are: assessment of the local findings; pathogen identification by culture of peripheral blood, swabs of the infected site, or material recovered at surgery; and transesophageal echocardiography to detect endocarditic deposits on the electrodes or cardiac valves. The treatment consists of appropriate antibiotic administration and the complete removal of all foreign material. These special extractions are generally performed via the transvenous route. With the aid of various sheath systems, the procedure can be carried out safely and effectively, with a success rate above 95% and a complication rate below 3%. The indications for the implantation of a new device after eradication of the infection should be critically reassessed.

Conclusion: Untreated infection carries a high mortality. Evaluation and treatment according to a standardized clinical algorithm facilitate correct and timely diagnosis and the choice of an appropriate therapeutic strategy.

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Cardiac implantable electronic devices (CIED), such as cardiac pacemakers (CP), implantable cardioverter defibrillators (ICD), and devices for cardiac resynchronization therapy (CRT), play an important role in the treatment of bradycardia arrhythmias, the prevention of sudden cardiac death, as well as in the treatment of heart failure (1). The annual number of new implantations in Germany has remained constant for years at around 105 000; however, at 356 ICD and 922 CP per 1 million inhabitants, more devices are being implanted in Germany than in any other European country (2–4) (*eTable*). This contrasts with the rising number of device replacements and revision procedures—most recently 50 000 per year—despite the fact that these are associated with a two- to four-fold increased risk of infection compared with primary implantation (3–7). Between 2004 and 2008, an increase was seen in the infection rate in the US from 1.53% to 2.41%, which can be explained by an expansion of ICD indications and an increasing number of implantations in patients with significant comorbidities (8). Furthermore, as a result of more frequent complex

CRT implantations, a 57% increase in infections was observed between 2004 and 2006, whereas the rise in the number of devices implanted was only 12% (9). Although absolute numbers on infection rates in Germany are lacking, there too one is seeing a considerable rise in CRT device implantations and patient age, with 42% of CP and 12% of ICD recipients currently aged over 80 years (3–6) (*eTable*).

As a result of extravascular and intravascular segments, infections can affect the device, the leads, or native cardiac structures. The updated guidelines issued by international specialty societies provide clear recommendations on the diagnosis and treatment of CIED infections; nevertheless, in the authors' experience, delayed diagnosis occurs even in specialized hospitals due to the diverse clinical presentation of these infections (10, 11). Unclear inflammatory constellations in CIED wearers should always prompt suspicion of infection, since timely treatment can prevent local infection with a hospital mortality of 2–5% from progressing to a systemic infection with 6–15%

TABLE 1

Risk factors for the development of infection

Risk factors	Relative risk [95% confidence interval]
Patient-related factors	
Terminal kidney failure	8.7 [3.4; 22.3]
Fever <24 h prior to implantation	5.8 [2.0; 17.0]
Corticosteroid therapy	3.4 [1.6; 7.3]
Kidney failure	3.0 [1.4; 6.6]
Chronic obstructive pulmonary disease	3.0 [1.8; 4.9]
Age >60 years	2.5 [1.2; 4.0]
Malignant disease	2.2 [1.3; 4.0]
Diabetes mellitus	2.1 [1.6; 2.7]
Heart failure	1.7 [1.1; 2.4]
Oral anticoagulation	1.6 [1.0; 2.5]
Female sex	0.7 [0.6; 0.8]
Surgery-related factors	
Postoperative hematoma formation	8.5 [4.0; 17.9]
Abdominal device pocket	4.0 [2.5; 6.5]
Temporary stimulation	2.3 [1.4; 3.9]
Previous infection	1.6 [0.9; 2.8]
>3 People in the operating theater	1.5 [0.8; 2.8]
Surgery time	1.0 [1.0; 1.1]
Perioperative antibiotic prophylaxis	0.3 [0.2; 0.6]
Implant-related factors	
≥ 4 Previous procedures	8.7 [3.6; 20.8]
Lead repositioning due to dislocation	6.4 [2.9; 13.8]
Revision procedures	2.0 [1.5; 2.7]
Device replacement	1.7 [1.2; 2.5]
Dual-chamber system	1.5 [1.0; 2.1]

Relative risk for the development of device-associated infection depending on various factors (modified from [17, 18, 20, 21, 39, e15]). The baseline risk for the development of infection is 0.5%–1% in the first 6–12 months following cardiac pacemaker implantation.

mortality. (12–14, e1). A relevant patient history should be taken and local findings assessed as part of the periodic device checks every 4–6 months.

With only a few exceptions, all infections represent an indication to remove the device and all implanted leads, in addition to appropriate antibiotic therapy (10). Due to its high success rate of 96.7% at a complication rate of 1.7–1.8% and an intraprocedural mortality rate of 0.3%–0.4%, interventional transvenous extraction is favored above surgical extraction (15, 16).

The aim of this article is to summarize current standards on the diagnosis and treatment of CIED infections and to formulate recommendations on routine practice for physicians active in the in- and outpatient setting.

Methods

This article is based on a selective literature search in PubMed using the search terms “cardiac AND implantable AND electronic AND device AND infection,” “pacemaker AND infection” and “lead AND endocarditis.” Since 2010, 963 articles have been published, 84 of which were evaluated. In addition, recommendations issued by the international specialty societies as well as data from the authors’ own literature collection are presented.

Incidence

The risk of infection following implantation of a CP is 0.5%–1% in the first 6–12 months and rises with increasing complexity of the implanted device (17). The infection rate for ICD implantations is 1.7% in the first 6 months and, at 9.5% after 2 years, even higher for CRT implantations (18, 19). Compared with primary implantation, the risk of infection in the case of device replacement or revision procedures is between two- and four-fold higher (7). Infections occurring within the first year following implantation or revision are generally due to bacterial contamination at the time of surgery. It has been shown that 25% of infections occur early (0–28 days postoperatively), 33% late (between 28 days and 1 year postoperatively), and 42% in a delayed manner (>1 year after the initial procedure) (e2). The rising number of device replacements results in complex procedures in older patients, sometimes with considerable comorbidities and a marked increase in infection rates (*Table 1*) (8, 17, 18, 20, 21).

Presentation and pathogenesis

The clinical picture of device-associated infections is diverse. They may affect the infraclavicular site of device implantation in the form of localized pocket infections, or the intravascular segment of the leads in the form of device-associated endocarditis (*Figure 1*). According to the authors’ estimate, localized infections account for the largest proportion (around 60%), and generally exhibit the classic signs of an inflammatory reaction at the implantation site, such as swelling, redness, and warmth. However, they can also follow a relatively mild course, thereby making diagnosis difficult (*Figure 1a*, *Table 2*) (22). Any swelling at the implantation site that is not in direct temporal conjunction with a surgical procedure is highly suspicious for infection. Perforation of the device through the skin equates to an infection as a result of subsequent colonization with skin bacteria (*Figure 1b*). Of the bacteria isolated, coagulase-negative staphylococci (42%–69%) and *Staphylococcus aureus* (14%–29%) are the most common pathogens; however, streptococci, enterococci, gram-negative bacteria, fungi, and anaerobes can also cause infections in rare cases. At 2.8%, the rate of methicillin-resistant *Staphylococcus aureus* (MRSA) is extremely low in Germany (25). Bacterial detection is not possible in 12%–21% of clinically diagnosed device-associated infections (14, e3).

Figure 1: Various findings in device-associated infection

Infection of the device pocket (a) is generally associated with typical clinical signs such as swelling, redness, and warmth. Perforation of the device through the skin (b) equates to an infection as a result of subsequent colonization with skin bacteria. Device-associated endocarditis is characterized by the detection of vegetation on transesophageal echocardiography (c) and pathogen detection in blood cultures (→ lead in right atrium; * endocarditis vegetation). In the case of device-associated infection without clear laboratory, clinical, or echocardiographic findings, 18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG-PET-CT) can contribute to establishing the diagnosis—evidence here of increased uptake (→) in the region of the left infraclavicular implantation site consistent with infection (d).

Bacterial colonization generally occurs at the time of implantation or revision surgery and goes on to become apparent as an infection within several weeks to months. If pathogens along the leads penetrate the blood stream, device-associated endocarditis involving bacterial colonization of the intravascular segment of the leads can occur (*Figure 1c*). Secondary infection due to hematogenous spread of bacteria originating from another focus of infection is also possible but rarer. Biofilm formation on the leads makes it difficult for the immunological defense mechanism or administered antibiotics to reach the pathogens and explains why definitive treatment is only possible by removing the entire system (e4).

Systemic infections exhibit non-specific symptoms such as fever, chills, night sweats, malaise, and weight loss; septic shock is seen in less than 10% of patients (*Table 2*) (26). Infections involving the intravascular segment of the leads account for around 10% of all cases of endocarditis (27). Despite appropriate treatment, lead-related endocarditis is associated with a hospital mortality rate of 6%–15%

and a 1-year mortality rate of 15%–23%, although no distinction can be made here between the effects of infection or concomitant comorbidities (12, 13, e5).

Diagnosis

Microbiological tests

Taking blood cultures is essential; at least three sets (aerobic/anaerobic) should be collected at intervals of not less than 30 min prior to initiating antibiotic therapy (28). Wound swabs should be taken, but are sterile in 15% of cases (29). The process of puncturing a closed pacemaker pocket to collect samples is obsolete. Intraoperative swabs from the device pocket and tissue samples should be analyzed along with the tips of the explanted leads (e6).

Echocardiography

Echocardiography plays a key role in diagnosis, since it is able to detect electrode or heart valve involvement, determine the size of vegetation, and quantify tricuspid valve insufficiency. Transthoracic echocardiography

TABLE 2

Clinical presentation of device-associated infection

Findings at the implantation site

Redness	41–68%
Swelling	38–67%
Secretion	38–50%
Pain	28–49%
Warmth	18–38%
Device/lead perforation	21–25%

Systemic inflammatory reaction

Fever >38 °C	43–45%
Malaise	28–42%
Chills	39–43%

Laboratory analysis

Anemia	50%
Leukocytosis	43%
Positive blood cultures	40–49%

Frequency of various local and systemic findings in patients with device-associated infection (modified from [14, 23])

(TTE) is able to assess prognostic parameters such as reduced left ventricular pump function, increased pulmonary arterial pressure, and the presence of pericardial effusion. Transesophageal echocardiography (TEE), with its sensitivity of 96% and specificity of 90% for the detection of endocarditis vegetation on leads or heart valves, is significantly superior to the transthoracic examination (*Figure 1c*) (e7). Both investigations should be performed in the case of suspected infection (11). Heart valve involvement is not limited to the tricuspid valve—vegetation is additionally found on the aortic or mitral valve in 10%–15% of cases of device-associated endocarditis. An echocardiographic examination should be performed as promptly as possible within the first 24 h. Approximately 45% of CIED carriers in whom *Staphylococcus aureus* is detected in blood cultures have a device-associated infection, meaning that these patients should undergo TEE (e8). Recurrent bacteremia without identification of a clear source of infection also represents an indication for device explantation even in the absence of echocardiographic detection of vegetation (10).

Laboratory diagnostics

Blood sampling and determination of leukocyte count, C-reactive protein (CRP), and erythrocyte sedimentation rate is mandatory, whereby laboratory inflammatory markers may be normal even if infection has been unequivocally detected. A procalcitonin (PCT) plasma level >0.05 ng/ml can predict localized infection with a sensitivity of 60% and a specificity of 82% (e9).

Positron emission tomography

In the case of clinical suspicion of CIED infection without guidance from echocardiographic or microbiological findings, 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) (18-FDG-PET-CT) can help to establish the diagnosis (30). This examination is also suited to detecting septic embolism in patients with device-associated endocarditis or detecting the primary source in hematogenously infected devices (e10). The routine use of 18-FDG-PET-CT in suspected device-associated infection is not recommended (*Figure 1d*).

Treatment

Treatment recommendations can be found in the current guidelines, whereby only a handful of randomized studies are available, meaning that recommendations are largely based on expert opinions (10).

Antibiotic therapy

A superficial wound infection that appears less than 30 days postoperatively, does not extend to the device, and shows no signs of systemic infection can be treated with 7- to 10-day antibiotic therapy alone. At 80%, the success rate for this antimicrobial therapy is high (31). Initial empirical antibiotic therapy in superficial infections of this kind, as well as isolated local pocket infections, should be initiated immediately following sample collection, cover the usual bacterial spectrum, and take local resistance into consideration, particularly with regard to MRSA prevalence. The treatment of device-associated endocarditis is based on the recommendations of the European Society of Cardiology (28). It is mandatory to adjust treatment following pathogen identification in swabs, surgical material, or blood cultures. The duration of antibiotic therapy depends on the severity and type of infection, as well as on the causal bacteria (*Figure 2*).

Transvenous lead extraction

Any infection involving the device and/or intravascular lead segments represents an indication for complete removal of all foreign materials (10, 32). At 38.2%, the 1-year mortality rate in patients receiving antibiotic therapy only for device-related endocarditis is almost twice as high as the rate with device explantation (19.9%) (12). Delayed device explantation following initial unsuccessful antibiotic therapy is also associated with a three-fold higher 1-year mortality rate compared with immediate explantation (13). Transvenous extraction of leads with less than 1 year dwell time is generally possible with simple traction.

When extracting older leads, tools such as locking stylets, a variety of extraction sheaths, and snares are used. Locking stylets are special mandrels coated with a thin wire mesh that are introduced into the central working channel of the lead. Expanding the wire mesh within the lead both stabilizes and lengthens the lead, thereby creating the appropriate conditions for

FIGURE

Recommendations on the diagnosis and appropriate treatment of device-associated infection (modified from [10, 26, 28, 40])

18-FDG-PET-CT, 18-fluorodeoxyglucose positron emission tomography/computed tomography; CRP, C-reactive protein; ICD, implantable cardiac defibrillator; PCT, procalcitonin

*¹ Generally as interventional transvenous lead extraction. An open surgical procedure can be considered in the case of vegetation > 2 cm on electrodes and is urgently indicated if surgery is already indicated due to valve endocarditis.

*² System explantation is indicated in the case of occult bacteremia with gram-positive pathogens. Likewise, in the case of recurrent bacteremia with gram-negative bacteria and no clear alternative focus of infection, system explantation needs to be considered.

*³ Antibiotic therapy according to the European Society for Cardiology's endocarditis guidelines (28).

*⁴ Antibiotic therapy for 4 weeks if *Staphylococcus aureus* is identified, 2 weeks for all other pathogens.

*⁵ Antibiotic therapy for 10 days in the case of dry pocket perforation, 14 days in the case of pocket infection. Empirical antibiotic therapy prior to pathogen detection should consist of vancomycin.

*⁶ Following a critical evaluation of the indication, re-implantation is required in only 67%–86% of patients.

the use of sheath systems (eFigure a). A variety of sheath systems can be used:

- Mechanical polypropylene sheaths that disrupt adhesions in the lead when rotated gently (eFigure b).
- An active extraction sheath with a metal thread and blade at the tip that can be rotated in a controlled

manner by pressing a release handle, thereby cutting the lead free (eFigure c).

- Laser sheath: a flexible plastic sheath with optically conductive fibers that is brought over the lead. When activated, the laser cuts the lead on the diode ring at the metal tip of the sheath in a circular fashion

The primary access selected for lead extraction is via the device pocket located in the infraclavicular region. If lead extraction is not possible from the implantation site, a femoral or jugular approach may be helpful (*eFigure d*) (22). Due to the potential for complications, procedures should only be performed in centers with a cardiac surgery unit, where they can be safely carried out with a high success rate (complete system removal in >95%) and a low surgical complication rate (16, 33). It has been shown that, in hospitals that perform fewer than 30 lead extractions per year, more complications occur (4.1% versus 2.4%; $p = 0.0146$), the success rate is lower (94.3% versus 97.3%; $p = 0.0001$), and mortality is higher (2.5% versus 1.2%; $p = 0.0088$) over the course of the inpatient stay (15).

The most frequent severe complication is myocardial injury (0.9%) followed by cardiac tamponade, which can be treated with pericardial puncture or surgical suturing of the perforation site. The most feared complication, superior vena cava laceration, occurs in 0.6% of cases and is associated with a mortality rate of >40% even in the case of immediate surgical treatment (15, e11). There is evidence that, by using a novel endovascular balloon catheter that occludes the vessel wall lesion, valuable time can be gained and mortality reduced from 50% to 0% (34). The overall perioperative mortality rate for interventional lead extraction is 0.5% (15).

Temporary stimulation in pacemaker-dependent patients by means of an external pacemaker connected to a percutaneously inserted right ventricular lead is required and safe until antibiotic therapy is completed and a new device is implanted (35). Microbiological analysis of lead tips and swabs obtained intraoperatively is absolutely essential in order to be able to initiate targeted antibiotic therapy in the case of pathogen detection.

Surgical extraction

Due to the risk of fulminant pulmonary embolism, open surgical extraction should be considered in the case of large vegetations (>20 mm) and is indicated if there is already a surgical indication due to valve endocarditis (36). As possible focuses of infection, implanted devices and leads should be removed during surgery for heart valve endocarditis, irrespective of whether they show signs of infection (10).

Re-implantation

The indication for renewed implantation needs to be reviewed critically using long-term ECG or telemetry monitoring, since 14%–33% of patients do not require a new device to be implanted following lead extraction. The most frequent reasons for this include: the criteria no longer being met for the original indication, inappropriate initial indication, or patient preference (23, 37). If re-implantation is indicated, this is performed on the contralateral side to the previous explanation. Novel forms of treatment such as subcutaneous

defibrillators or intracardiac pacemakers should be considered and used where appropriate. The timing of re-implantation depends on the severity of infection as well as the responsible bacterium and can only be performed once adequate antibiotic therapy has been completed (*Figure 2*).

Prevention of device-associated infection

Risk factors for the development of device-associated infection (*Table 1*) need to be minimized preoperatively. Preoperative antibiotic prophylaxis significantly reduces the infection rate and, as such, should be administered in all procedures (31). An absorbable antibacterial envelope that encases the device and extravascular leads and releases antibiotics to the surrounding tissue showed a risk reduction of 71% for the development of infection in a meta-analysis (38). This envelope should be deployed particularly in procedures with high risk of infection, such as device replacement or other revision procedures (e12). Drug prophylaxis for infective endocarditis in procedures bearing a potential risk for bacteremia is not recommended in CIED patients (28).

Summary

CIED infections are becoming ever more frequent and, without adequate treatment, are associated with high mortality. Diagnosis can be challenging due to the diverse clinical picture of infections and one always needs to rule out involvement of other cardiac structures. Definitive treatment consists of complete removal of the entire system, which can be performed safely and successfully in specialized centers using a transvenous approach. Device re-implantation is not necessary in all patients; however, when required, it should be carried out on the contralateral side following adequate antibiotic therapy over a sufficiently long period of time

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Key messages

- Device replacement and revision procedures are associated with a two- to four-fold higher risk of infection compared with primary implantation. Procedures of this kind are increasingly being performed in Germany (currently approximately 50 000 per year).
- Due to the diverse clinical picture, which can range from localized infection of the device and extravascular lead segments to device-associated endocarditis and infection of the intravascular lead segments or other cardiac structures, correct diagnosis is challenging and, in the authors' experience, often delayed.
- In terms of diagnosis, the most important methods include transesophageal echocardiography to detect endocarditis vegetation, pathogen detection in blood cultures, swabs, and surgical materials.
- Treatment always consists of adequate antibiotic treatment and complete removal of all foreign materials, whereby lead extraction can be performed using minimally invasive transvenous methods in specialized centers with success rates >95% and complication rates <3%.
- It is not always necessary to re-implant a cardiac implantable electronic device. However, where necessary, this should be performed on the contralateral side following the completion of antibiotic therapy.

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► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref2618

eFigures, eTables:
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CLINICAL SNAPSHOT

Penile Mondor's Disease Triggered by May-Thurner Syndrome

A 30-year-old man presented with recurrent, painful swelling of the penis. He credibly denied self-manipulation or the use of sex toys. Clinical and duplex ultrasonographic examination revealed thrombosis of the dorsal penile vein (Figure). Thrombosis at this site is designated as penile Mondor's disease. In addition, an anatomical compression of the left common iliac vein by the right common iliac artery was visualized. This hemodynamically relevant stenosis (so-called May-Thurner syndrome) was dilated with balloon angioplasty and stent implantation. The patient was then treated for three months with a factor Xa inhibitor. The penile swelling regressed immediately after the intervention, and a complete recovery ensued over the following four weeks.

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Supplementary material to:

The Diagnosis and Treatment of Pacemaker-Associated Infection

by Michael Döring, Sergio Richter, and Gerhard Hindricks

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eTABLE

Number of procedures in Germany

	2010	2011	2012	2013	2014	2015
PM implantations, n	73 778	75 702	76 233	75 575	76 169	75 730
Percentage of CRT-P	1.1	1.2	1.5	1.8	2.2	3.2
PM device replacement, n	16 517	16 704	17 229	17 740	18 389	18 725
PM revisions, n	13 003	13 556	13 447	13 525	13 492	12 209
Age of females with PM (years)	77.8	77.7	77.6	77.5	77.8	*
Age of males with PM (years)	74.6	74.8	75.0	75.1	75.3	*
ICD implantations, n	25 582	28 452	29 574	29 458	29 620	30 002
Percentage of CRT-D	28.2	29.9	31.3	33.2	33.5	33.2
ICD device replacement, n	6002	6818	7059	8419	9357	10 078
ICD revisions, n	7014	8056	8786	9160	9618	9384
Age of females with ICD (years)	65.6	66.5	66.3	66.8	66.9	*
Age of males with ICD (years)	66.0	66.3	66.4	66.7	67.0	*
New implantations (all CIED), n	99 360	104 154	105 807	105 033	105 789	105 732
Device replacement (all CIED), n	22 519	23 522	24 288	26 159	27 746	28 803
Revisions (all CIED), n	20 017	21 612	22 233	22 685	23 110	21 593
Percentage of all revisions (%)	42.8	43.3	44.0	46.5	48.1	47.7

Number of new implantations, device replacements, and revision procedures for cardiac pacemakers (PM) and implantable cardioverter defibrillators (ICD) in Germany in the period 2010–2015. What is striking is that, while the number of new implantations remained consistent, the percentage of revision procedures (including device replacement) for all cardiac implantable electronic devices (CIED) increased (from 42.8% in 2010 to 47.7% in 2015), as did the number of complex CRT implantations (3–6, e13, e14).

CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy—defibrillator; CRT-P, cardiac resynchronization therapy—pacemaker; n, number; * not specified

eFigure: Various tools used for lead extraction

- a) A locking stylet (*), inserted in a right atrial lead, is used to stabilize and lengthen the leads. A right ventricular lead (+) and an occluder in the left atrial auricle (‡) are visualized as secondary findings.
- b) Mechanical polypropylene extraction sheaths, which are available in a variety of sizes, are advanced to the tip of the ICD lead to be extracted (*) in order to disrupt adhesions. A temporary catheter (+) in the right ventricular apex ensures stimulation in pacemaker-dependent patients.
- c) A mechanically controlled rotating extraction sheath with a rotating blade at the tip (*) is used to extract a right arterial lead.
- d) Snares are used to extract leads via a femoral or jugular approach. An ICD lead (*) trapped in the right ventricle is extracted via a right jugular approach (+). Lead in the right atrium, (‡) Seldinger wire in the left subclavian vein to secure the vessel lumen.