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Usefulness of Sonication of Cardiovascular Implantable Electronic Devices to Enhance Microbial Detection

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Abstract

The cardiovascular implantable electronic device (CIED) infection rate is rising disproportionately to the rate of device implantation. Identification of microorganisms that cause CIED infections is not always achieved using present laboratory techniques. We conducted a prospective study to determine whether device vortexing-sonication followed by culture of the resulting sonicate fluid would enhance microbial detection compared with traditional swab or pocket tissue cultures. Forty-two subjects with noninfected and 35 with infected CIEDs were prospectively enrolled over 12 months. One swab each from the device pocket and device surface, pocket tissue, and the CIED were collected from each patient. Swabs and tissues were cultured using routine methods. The CIED was processed in Ringer's solution using vortexing-sonication and the resultant fluid semiquantitatively cultured. Tissue and swab growth was considered significant when colonies grew on 2 quadrants of the culture plate and device was considered significant when 20 colonies were isolated from 10 ml of sonicate fluid. In noninfected group, 5% of sonicate fluids yielded significant bacterial growth, compared with 5% of tissue cultures ($p = 1.00$) and 2% of both pocket and device swab cultures ($p = 0.317$ each). In infected group, significant bacterial growth was observed in 54% of sonicate fluids, significantly greater than the sensitivities of pocket swab (20%, $p = 0.001$), device swab (9%, $p < 0.001$), or tissue (9%, $p < 0.001$) culture. In conclusion, vortexing-sonication of CIEDs with semiquantitative culture of the resultant sonicate fluid results in a significant increase in the sensitivity of culture results, compared with swab or tissue cultures.

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Disclosures

The remaining authors have no disclosures.

The cardiovascular implantable electronic device (CIED) implantation rate has markedly increased, largely because of expanding indications for device implantation.¹ This has been accompanied by an increasing rate of device infections.^{2–4} Infection is a serious complication of CIED implantation that necessitates device removal through percutaneous or surgical approach that is associated with significant morbidity and mortality and considerable financial burden for the patient and the health care system.^{5–7} Current guidelines recommend generator pocket tissue Gram stain and culture and lead-tip culture for identification of the causative microorganism(s).⁸ However, Gram stain has been shown to have limited utility in the diagnosis of device-related infections,⁹ and cultures may be negative for a variety of reasons, including concentration of organisms in biofilms on the device surface and consequently not in the surrounding tissue and the presence of so-called “small colony variants” that may be more difficult to isolate by routine cultures.^{10–12} Vortexing-sonication of implants followed by culture of the resultant sonicate fluid is more sensitive and specific compared with conventional periprosthetic tissue culture for the diagnosis of prosthetic joint infection.^{13,14} Consequently, this technique has been adopted in clinical microbiology laboratories across the world for the diagnosis of prosthetic joint infection. On the basis of findings from these investigations, we hypothesized that vortexing-sonication, followed by culture of the resulting sonicate fluid, will enhance microbial detection compared with traditional swab or pocket tissue culture for the diagnosis of CIED infection.

Methods

The study was conducted at Mayo Clinic, Rochester, from November 2011 to November 2012. Potential subjects were identified using the institutional operating room census and by direct communication with the electrophysiology and cardiac surgical services. Written informed consent was obtained from all study subjects. For patients who consented for participation and underwent explantation of a CIED, the following samples were collected: (1) CIED; (2) device surface swab; (3) pocket tissue swab; and (4) pocket tissue (~1 cm³ in size). The Mayo Clinic Institutional Review Board approved the study protocol.

CIED infection was defined as the presence of inflammatory changes (erythema, warmth, fluctuation, or purulent discharge) at the generator pocket site, persistently positive blood cultures in the absence of any other defined focus of infection or pathologic analysis of pocket tissue demonstrating acute inflammation. *CIED-related endocarditis* was defined on the basis of modified Duke criteria.^{15,16} Device generator or leads that eroded through the pocket were also classified as infected. We concurrently enrolled subjects with no clinical or pathologic signs of infection, typically patients who underwent replacement of a generator for “end of battery life,” as noninfected controls.

The swabs and tissues were subjected to routine microbiologic culture involving inoculation onto aerobic blood and chocolate agars, and in cases of tissues, onto anaerobic blood agar and into thioglycollate broth (BD Diagnostic Systems, Sparks, Maryland) as well. Aerobic and anaerobic sheep blood agar plates (BD Diagnostic Systems) were incubated at 35°C to 37°C in 5% to 7% CO₂ aerobically and anaerobically for 4 and 7 to 14 days, respectively. Cloudy thioglycollate broth was subcultured.

The cardiac device was sent to the laboratory in a sterile 1-liter, straight-sided, wide-mouthed polypropylene (Nalgene) jar. Four hundred milliliters of Ringer's solution was added to the container. The container was vortexed for 30 seconds using a Vortex Genie (Scientific Industries Inc., Bohemia, New York) and then subjected to sonication (frequency 40 ± 2 kHz, power density 0.22 ± 0.04 W/cm²) in 5510 model ultrasound bath (Branson Ultrasonics Corp., Danbury, Connecticut) for 5 minutes, followed by vortexing for an additional 30 seconds (Figure 1). Fifty milliliters of sonicate fluid was placed into a conical tube and centrifuged at $\times 3,150g$ for 5 minutes. The supernatant was aspirated leaving 0.5 ml remaining in the tube, 0.1 ml which was plated onto an aerobic and another 0.1 ml onto an anaerobic sheep blood agar plate which were incubated at 35°C to 37°C in 5% to 7% CO₂ aerobically for 4 days and anaerobically for 14 days. Microorganisms were enumerated and classified using routine microbiologic techniques (Figure 2).

Host demographics, comorbidities, clinical signs and symptoms, laboratory parameters, and microbiologic results were collected using a data collection instrument and entered into a REDCap version 4.13.17 (Vanderbilt University, Nashville, Tennessee) database.¹⁷

Sensitivity and specificity were calculated for device, swab, and tissue cultures, with infection status (gold standard) defined by clinical and pathologic criteria described previously. Device sonicate fluid cultures were classified as a positive versus negative result on the basis of a cut-off point of <20 colony-forming units/10 ml (CFU/10 ml) derived from a previous validation study of prosthetic joint infections at our institution.¹⁸ To test whether device sonicate fluid culture had greater sensitivity or specificity than each of the swab or tissue cultures for the diagnosis of CIED infection, McNemar test of paired proportions was used. A p value <0.05 was considered statistically significant. All analyses were performed using the SAS statistical software package version 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

Ninety-three subjects were enrolled, of which 16 were excluded because of gross contamination of specimens during device extraction, specimen transportation delay of more than 12 hours, or failure to collect the requisite specimens. Of the 77 subjects included in the final analysis, 35 met the criteria for CIED infection and 42 were considered uninfected. There were no statistically significant differences in host, demographic, or clinical characteristics between these 2 groups (Table 1) although infected subjects had marginally higher rates of diabetes (34 vs 17%, $p = 0.074$), chronic kidney disease (stage 3 or greater/ glomerular filtration rate <60 ml/min/1.73 m²; 29 vs 12%, $p = 0.066$), and previous history of CIED infection (14 vs 2%, $p = 0.052$).

In the infected group, there were 12 cases of pocket cellulitis, 4 cases of device or lead erosion (without clinical signs of cellulitis around the pocket or positive blood cultures), 14 cases of bloodstream infection, presumably involving the intravascular portion of the lead(s), and 5 cases of CIED-related bloodstream infection simultaneously involving native or prosthetic heart valve(s) (Figure 3). Twenty-nine (83%) subjects (4 with pocket infection

and 2 with device erosion) had received antibiotic therapy before cardiac device extraction and specimen collection.

In the noninfected group, a number of culture plates yielded microbial growth, typically with low numbers of colonies (i.e., growth in the first quadrant/1 + growth/growth in broth only) of low-virulence organisms such as *Bacillus* sp., *Corynebacterium* sp., or *Propionibacterium* sp., which were likely representative of contamination. Moreover, comparing all specimens from each patient, none of the subjects had consistent growth of the same organism across all 4 specimens analyzed.

Because causative organisms (most commonly *Staphylococcus aureus* or Coagulase-negative *Staphylococcus*) were known in cases of lead or valve endocarditis on the basis of persistently positive blood cultures, we analyzed the level of discordance between blood culture results and cultures of the specimens removed at the time of device removal. Of 19 cases of lead or valve endocarditis, sonicate fluid culture results were discordant with blood culture results in 3 subjects. Tissue and/or swab culture results were also discordant with the results of the blood cultures in 3 subjects. Results of both sonicate fluid and tissue/swab culture results were different from those of blood culture in 2 subjects, whereas 1 patient had discordant results exclusively with the sonicate fluid and another exclusively with the tissue/swab cultures.

Comparative results of sensitivity and specificity across different culture types are summarized in Table 2. Although in noninfected subjects, 40% of sonicate fluids yielded any microbial growth on culture, compared with 33% of tissues ($p = 0.366$), 7% of pocket swabs ($p < 0.001$), and 5% of device swabs ($p < 0.001$), when disregarding minimal growth likely to represent contamination (i.e., < 20 CFU/10 ml sonicate fluid and 1 + growth or growth in broth only for swab and tissue cultures, hereafter considered nonsignificant), 5% of sonicate fluids yielded a positive microbiologic result, compared with 5% of tissue cultures ($p = 1.00$) and 2% of both pocket and device swab ($p = 0.317$ each) cultures. Also based on significant positive growth, the overall sensitivity of sonicate fluid culture (54%) was greater than that of pocket swab (20%, $p = 0.001$), device swab (9%, $p < 0.001$), and tissue (9%, $p < 0.001$) culture.

Subgroup analyses revealed evidence that the device sonicate fluid culture was generally more sensitive than the other tests in the infected subset with device erosion/pocket cellulitis and lead or valve endocarditis (Table 3). For the 16 cases of device erosion/pocket cellulitis, sensitivity of either swab or tissue culture (based on significant positive growth) was only 38% (95% confidence interval [CI], 15% to 65%) compared with 69% (95% CI 41% to 89%) for device sonicate fluid culture ($p = 0.059$). For the 19 cases of lead or valve endocarditis, sensitivity of either swab or tissue culture (based on significant positive growth) was only 11% (95% CI 1% to 33%) compared to 42% (20% to 67%) for device culture ($p = 0.014$).

Discussion

The present investigation is the largest and provides the most comprehensive description of a vortexing-sonication technique in clinical practice to enhance microbial detection in cases of CIED infection. Recent guidelines issued by the American Heart Association⁸ recommend swab and tissue Gram stain and cultures to identify pathogens. However, several factors impact Gram stain and culture yield.

Vortexing-sonication of prosthetic orthopedic devices has been shown to be more sensitive than periprosthetic tissue culture for the diagnosis of prosthetic joint and implant infections.^{13,14,19,20} Our study findings suggest that sonication is superior to device or pocket swabs and pocket tissue cultures, techniques that are routinely used for establishing a microbiologic diagnosis, irrespective of the type of CIED infection.

Although 5% of sonicate fluid cultures in our study revealed significant bacterial growth from noninfected devices, there was some growth from 40% of noninfected devices overall. The significance of this finding, which appears to be a repetitive theme in similar studies,^{21–25} is unclear.²⁶ In this investigation involving CIEDs, as with our previous prosthetic joint infection studies, the low virulence of isolated microorganisms and the small quantity of growth observed in most noninfected cases were considered consistent with contamination. Therefore, after adjudicating these cultures with small quantity of growth as possible contaminants, our estimated specificity of device sonicate fluid cultures was 95%, similar to that of swab (98%) and tissue (95%) cultures.

False-positive microbiologic results are also a theoretical concern in clinically infected devices. Contamination of CIEDs can occur at the time of collection, during transport, specimen processing, or during incubation. To address this possibility, we compared positive results from various specimens (swabs, tissues, and sonicate fluid) with those of blood cultures in cases of CIED lead or valve endocarditis. In the 19 cases with definite lead or valve endocarditis, results of device sonication cultures differed from blood cultures in only 3 cases. This was similar to a discrepancy between blood cultures and swab or tissue cultures. Therefore, the likelihood of a positive sonicate fluid culture representing a false-positive result does not seem to be greater than that of false-positive results from traditional swab or tissue cultures.

Despite the use of sonication technique, some cultures from clinically infected devices also resulted in bacterial growth in small numbers. Although we classified these results as representing contamination based on our predefined cut-off values, it is possible that in some cases, these results represent true pathogens as 83% of subjects with CIED infection had received antibiotics before device explantation and collection of specimens for cultures.

Usefulness of vortexing-sonication technique for the microbiologic diagnosis of CIED infections has been evaluated in earlier investigations (Table 4).^{22,24,25} However, these studies were limited by relatively small numbers of patients with infected devices, and there were no attempts to explain or eliminate the possibility of false-positive cultures results observed with either of the culture techniques. Because all positive culture results in these studies were considered to represent true infection, they may have overestimated the

sensitivity of both sonication and traditional culture techniques. In contrast, we have tried to make a clear distinction between results that are likely to represent pathogens versus those that represent contamination.

Overall, our study findings suggest that vortexing-sonication of CIEDs with semiquantitative culture of the resultant sonicate fluid results in a significant increase in the sensitivity of culture results, compared with swab or tissue cultures, without compromising the specificity of positive results when only significant growth is deemed true positive. Results of this study should influence the future guidelines regarding diagnostic evaluation of CIED infection.

There are several limitations of present investigation, the most important being the small number of subjects. However, considering the generally low rates of CIED infections, this is the largest cohort of patients with infected CIED systems in which sonication technique has been used for microbial detection. The implication of a positive sonicate fluid culture in couple of subjects in the noninfected group remains unclear, and we are prospectively following these patients to see if they develop a clinically overt CIED infection. Another limitation in our study cohort was initiation of antimicrobial therapy before the collection of specimens for cultures. However, this should have affected the results of all culture techniques studied, regardless of specimen type. Moreover, this is a true representation of current practice of medicine where initiation of treatment cannot always be withheld before collection of specimens because of unstable clinical condition of subjects with device infection, especially those with systemic signs and symptoms or evidence of bloodstream infection, or because of infections at other sites. Finally, our study population consisted largely of Caucasian patients, reflective of the general demographic of the population served at our institution. However, considering that the focus of our investigation was isolation of microorganisms rather than studying host response, we do not anticipate that results will vary on the basis of inclusion of more ethnically diverse patient populations.

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Figure 1. Apparatus for sonication. (A) Autoclaved container used for transportation and sonication of cardiac device; (B) vortexing apparatus; and (C) sonicator.

Figure 2. Colony-forming units visualized on standard blood agar culture plate following (A) device (sonicate fluid) culture; (B) swab culture; and (C) tissue culture from 1 study subject.

Figure 3.
Clinical presentation of patients with CIED infection.

Table 1

Demographic and clinical characteristics of infected and non-infected cardiovascular implantable electronic device groups

Demographic Characteristic	Infected* (n=35)	Non-infected* (n=42)	p-value
Age (in years)	63.7±17.3	67.4±15.4	0.319
BMI (kg/m ²)	31.1±7.0	29.2±7.2	0.270
Men	24 (69%)	25 (60%)	0.411
White	33 (94%)	41 (98%)	0.588*
Hypertension	21 (60%)	24 (57%)	0.800
Hyperlipidemia	23 (66%)	30 (71%)	0.590
Diabetes Mellitus	12 (34%)	7 (17%)	0.074
Chronic Kidney Disease (GFR <60)	10 (29%)	5 (12%)	0.066
Immunosuppression	4 (11%)	1 (2%)	0.109
Coronary Artery Disease	20 (57%)	18 (43%)	0.212
Cerebrovascular Disease	5 (14%)	4 (10%)	0.517
Peripheral Vascular Disease	2 (6%)	1 (2%)	0.588*
Chronic Obstructive Pulmonary Disease	4 (11%)	4 (10%)	0.785
Prosthetic Valve	8 (23%)	6 (14%)	0.332
Prior CIED Infection	5 (14%)	1 (2%)	0.052
Atrial Fibrillation	9 (26%)	17 (40%)	0.173
Heart Failure	21 (60%)	20 (48%)	0.278

Continuous data summarized with mean±SD, and compared between groups via two-sample *t* test; categorical variables reported with counts and percentages, and compared using the Chi-square test unless specified otherwise.

BMI = Body Mass Index; CIED = Cardiovascular Implantable Electronic device; GFR = Glomerular Filtration Rate (in mL/min); HDL = High Density Lipoprotein (in mg/dL); LDL = Low Density Lipoprotein (in mg/dL), HDL = High Density Lipoprotein (in mg/dL), GFR = Glomerular Filtration Rate (in mL/min).

Definitions: Hypertension was defined as blood pressure greater than 140/90 mm Hg, Hyperlipidemia was defined as Low Density Lipoprotein >160 mg/dl or High Density Lipoprotein <40 mg/dl. Coronary artery disease was defined as previously documented evidence of angina pectoris, myocardial infarction, history of angioplasty for coronary artery obstruction or history of coronary artery bypass grafting.

* p-value from Fisher's exact test due to sparse data.

Table 2

Sensitivity and specificity of culture for cardiovascular implantable electronic device infection based on the specimen-types studied

Test	Proportion	Sensitivity Rate, % (95% CI)	P-value *	Proportion	Specificity Rate, % (95% CI)	P-value *
Significant Growth						
Device Swab	3/35	9 (2-23%) [†]	<.001	41/42	98 (87-100%)	0.317
Pocket Swab	7/35	20 (8-37%) [†]	0.001	41/42	98 (87-100%)	0.317
Tissue	3/35	9 (2-23%) [†]	<.001	40/42	95 (84-99%)	1.000
Sonicate Fluid	19/35	54 (37-71%)		40/42	95 (84-99%)	
Any Growth						
Device Swab	10/35	29 (15-46%) [†]	<.001	40/42	95 (84-99%) [†]	<.001
Pocket Swab	15/35	43 (26-61%) [†]	0.008	39/42	93 (81-99%) [†]	<.001
Tissue	16/35	46 (29-63%) [†]	0.004	28/42	67 (50-80%)	0.366
Sonicate Fluid	26/35	74 (57-88%)		25/42	60 (43-74%)	

* p-value testing for a difference in performance rate relative to sonicate fluid culture via McNemar's test.

[†] Value is significantly different from that by sonicate fluid culture (p <0.05 from McNemar's test).

Table 3

Sensitivity of culture based on the specimen types studied among patients with cardiovascular implantable electronic device infection; stratified based on subgroups with a) device erosions and pocket infections and b) lead or valve associated endocarditis

Test Subgroup	Sensitivity					
	Proportion	Rate, % (95% CI)	P-value *	Proportion	Rate, % (95% CI)	P-value *
Device Erosions/Pocket Infections (n=16)		Significant Growth			Any Growth	
Device Swab	2/16	13 (2-38%) [†]	0.003	6/16	38 (15-65%) [†]	0.035
Pocket Swab	5/16	31 (11-59%) [†]	0.034	10/16	63 (35-85%)	0.257
Tissue	2/16	13 (2-38%) [†]	0.003	10/16	63 (35-85%)	0.180
Sonicate Fluid	11/16	69 (41-89%)		13/16	81 (54-96%)	
Lead or Valve associated Endocarditis Infections (n=19)		Significant Growth			Any Growth	
Device Swab	1/19	5 (0-26%) [†]	0.008	4/19	21 (6-46%) [†]	0.003
Pocket Swab	2/19	11 (1-33%) [†]	0.014	5/19	26 (9-51%) [†]	0.011
Tissue	1/19	5 (0-26%) [†]	0.008	6/19	32 (13-57%) [†]	0.008
Sonicate Fluid	8/19	42 (20-67%)		13/19	68 (43-87%)	

* p-value testing for a difference in performance rate relative to sonication via McNemar's test.

[†] Value is significantly different from that by Sonication test (p <.05 from McNemar's test).

Table 4

Literature review of the microbiological yield of sonicate fluid and swab/tissue cultures

	Number of subjects with CIED infection	Sensitivity of sonicate fluid culture [*]	Sensitivity of swab/tissue culture [*]
Present study [*]	35	54%	9–20%
Oliva et al. ²⁴	20	67%	50%
Mason et al. ²⁵	16	94%	75–81%
Rohacek et al. ¹⁴	6	100%	67%

^{*} Values represent sensitivity of cultures for detecting significant growth.