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Pathologic Findings Related to the Lead System and Repeated Defibrillations in Patients With the Automatic Implantable Cardioverter-Defibrillator

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The purpose of the present study was to examine at autopsy the effect of multiple defibrillations on the myocardium and the pathologic consequences of short- and long-term placement of the intravascular and interpericardial leads of the automatic implantable cardioverter-defibrillator. Twenty-five patients were examined at autopsy; 8 of them underwent lead implantation only and 17 received both leads and the automatic implantable cardioverter-defibrillator. Twelve patients (48%) died of ventricular tachycardia or ventricular fibrillation; seven (28%) died of other causes.

Acute pericarditis occurred in all patients, resulting in a localized, progressive fibrosis around the apical patch lead without giving rise to pericardial restriction. Thrombus formation was associated with the superior vena cava spring electrode in four patients (17%) and the right ventricular rate-sensing electrode in one patient (4%). Asymptomatic pulmonary emboli occurred in two patients (8%). In one patient who underwent defibrillation 59 times, superior vena cava changes consisted of vein wall destruction, fibrosis and thrombus formation.

Pathologic changes under the apical patch related to defibrillation were observed in seven patients; two of these had fewer than 5 defibrillations, one had 8 defibrillations and four had 21 to 74 defibrillations. These changes consisted of contraction band necrosis in four patients, vacuolar cytoplasmic clearing and loss of myocytes confined to the myocardium under the patch electrode in five patients who had multiple defibrillations. The observed pathologic changes were estimated to affect <2% of the total myocardial mass. Thus, the automatic implantable cardioverter-defibrillator lead system and multiple defibrillations result in localized myocardial injury confined to the tissue under the patch electrode. Superior vena cava lead-associated thrombosis may occur as with other long-term implanted transvenous catheters.

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The automatic implantable cardioverter-defibrillator is an electronic device capable of detecting and treating ventricular tachycardia and ventricular fibrillation. The device and its lead system have been described elsewhere (1–3). Although improved survival from ventricular tacharrhythmias with this device has been documented previously, information regarding the pathologic consequences of the electrode placement and the effect of repeated defibrillations in humans has not been described in any appreciable number of patients (2,3).

The effects of the leads and the consequences of repeated defibrillations would be anticipated to produce the following: 1) direct effect of repeated discharges on the myocardium and vascular structures, 2) possible thrombogenic potential of the indwelling intravascular electrodes, and 3) pericardial changes due to the pericardiotomy and placement of the apical patch electrode intrapericardially. Previous investigators (4,5) have pointed out that gross pathologic changes can be observed in the myocardium directly under

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the external defibrillator electrodes in dogs with higher levels of direct current energy discharges. These changes are related to the energy delivered, paddle size and the time interval between discharges (6). The effects of repeated internal defibrillator discharges on the myocardium in human subjects are unknown.

Thromboembolic complications have been described in association with indwelling, permanent pacemaker leads (7–9). Although the incidence of symptomatic thrombosis is rare, the prevalence of asymptomatic partial or complete obstruction in the superior vena cava is much more common and occurs in a significant number of patients with indwelling pacemaker leads (10,11). The larger size of the superior vena cava lead used for the anode of the automatic implantable cardioverter-defibrillator would be expected to provide a more significant impedance to flow in the subclavian vein and superior vena cava, possibly resulting in a higher incidence of asymptomatic and symptomatic thrombosis.

The apical patch electrode, which functions as the cathode of the defibrillating electrode pair, is most often placed intrapericardially either at open thoracotomy, if additional cardiac surgery is required, or from a subxiphoid incision if the defibrillator is implanted (12). Pericarditis associated with pericardiotomy and cardiac surgery is an expected pathologic finding. However, additional changes that may result from long-term implantation of the apical patch electrode are unknown. The objective of the present study was to examine retrospectively pathologic changes at autopsy due to short-term and long-term electrode implantation and multiple internal defibrillations in patients treated with the automatic implantable cardioverter-defibrillator.

Methods

Study patients. A total of 159 survivors of sudden cardiac arrest received an automatic defibrillator (either an AID or an AICD model) between February 1980 and November 1985 at the Johns Hopkins and Sinai Hospitals, Baltimore, Maryland. An additional 43 patients underwent only lead implantation together with another cardiac surgical procedure such as coronary bypass graft surgery, subendocardial resection, aneurysmectomy, mitral valve replacement or various combinations of these procedures in anticipation of eventual generator placement. In most cases the leads were placed at the time of surgery so that if the antiarrhythmic drug therapy failed, the lead system, already in place, could be easily connected to an automatic implantable cardioverter-defibrillator without an additional thoracotomy.

During this period, a total of 56 patients died, 37 with an automatic implantable cardioverter-defibrillator and 19 with implanted leads only. Of the 25 patients in whom an autopsy was performed, 17 had the automatic defibrillator and 8 had implanted leads alone (Table 1). The mean age of the 56 patients was 56 ± 14 years (± SD); 21 were male and 4 female. Twenty patients had coronary artery disease, three had congestive cardiomyopathy, one had hypertrophic cardiomyopathy and one had mitral valve prolapse. The mean left ventricular ejection fraction was 32 ± 17%. This group of patients, although highly selected, is representative of the group as a whole in terms of both the etiology of the underlying disease and other clinical variables, including the age and the sex distribution.

Table 1. Sudden Cardiac Death Survivor Population (February 1 to November 30, 1985)

	AID or AICD (n = 159)	Leads and Associated Cardiac Surgery (n = 43)
Alive	122	24
Dead	37	19
No autopsy	20	11
Autopsy	17	8

AICD = automatic implantable cardioverter-defibrillator; AID = automatic implantable defibrillator.

Twelve patients (48%) died of incessant ventricular tachycardia or ventricular fibrillation, and seven (28%) died of left ventricular failure manifested by pulmonary edema or cardiogenic shock. Six patients (24%) died of other causes: one patient died secondary to a vascular tear and hemothorax caused by insertion of a pulmonary artery catheter for intraoperative monitoring, two patients died secondary to sepsis, two patients had an intraoperative myocardial infarction and could not be successfully weaned from cardiopulmonary bypass and one patient had fulminant non-A, non-B hepatitis that led to irreversible hepatic failure and death.

Pathology. All available pathologic materials were reviewed. The hearts of 15 patients were examined after postmortem angiography and fixation in distension (13). However, in all 25 patients histologic sections of the representative sections of myocardium and pericardium were examined. Additional histologic specimens were prepared to more clearly document changes related to the placement of the electrodes in the 15 available gross specimens. The amount of myocardial tissue affected by defibrillation was visually estimated from review of the whole heart and histologic specimens.

Results

Pathologic changes related to the apical patch electrode (Fig. 1). Two patients died within 24 hours of the placement of the apical patch electrode. Histologic changes in these patients were limited to thin fibrin layer deposition in the pericardial-epicardial interface. In two patients who died after 24 hours but within 1 week of surgery (mean 6 days), early organizing pericarditis with infiltration of poly-

JACC Vol. 10, No. 2
August 1987:382–8

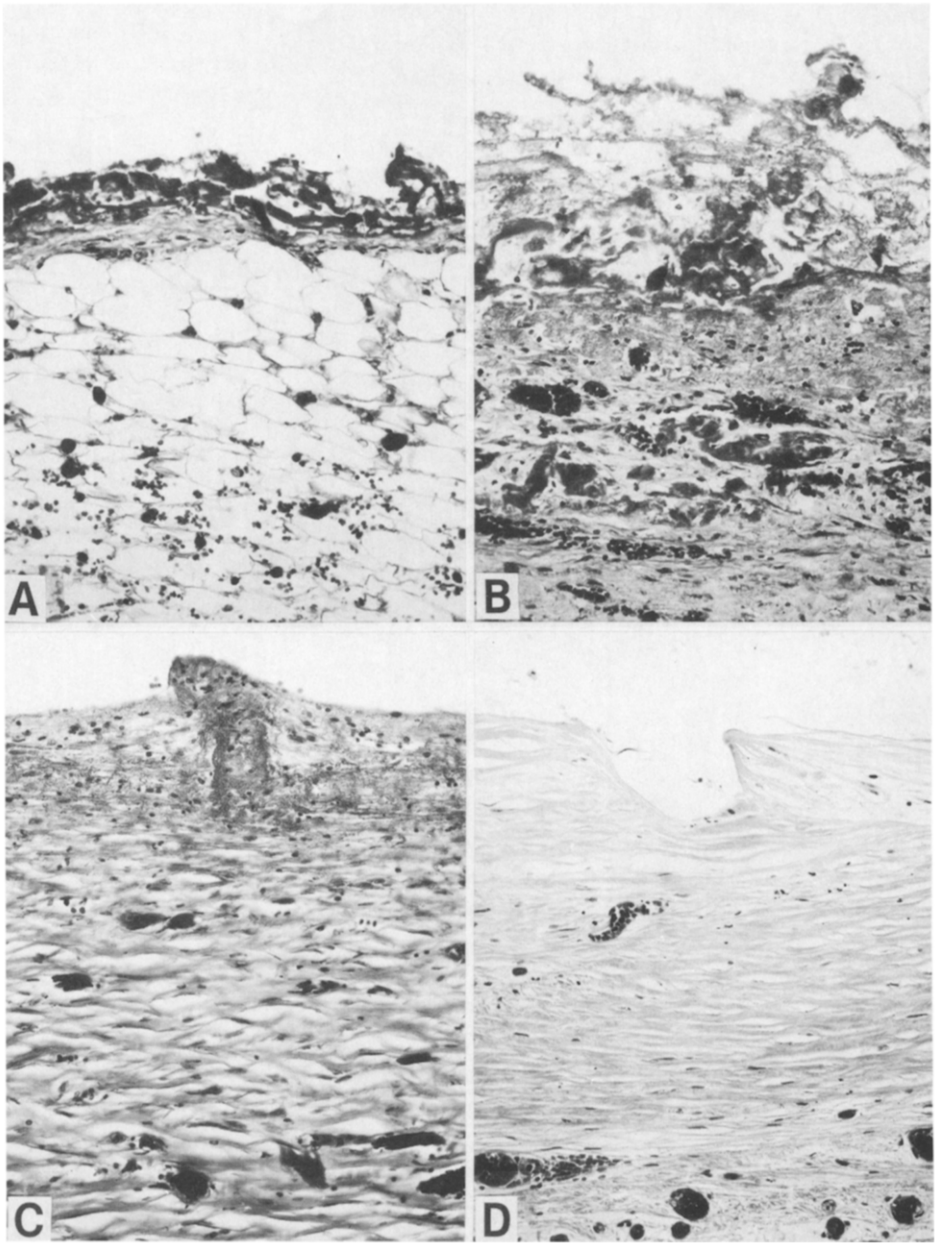


Figure 1. Sequential postoperative changes in the epicardial tissues beneath the patch in four patients at **(A)** 5 days, **(B)** 12 days, **(C)** 39 days and **(D)** 696 days. The fibrin deposit progressively thickens, becomes organized and thins again in its mature collagenized state. (Hematoxylin-eosin stain; original magnification ×200; reduced by 30%.)

morphonuclear cells and pericardial to epicardial adhesions was seen. Five patients died within 1 month (mean 20 days) of the apical patch placement. In these patients, organized pericarditis with round cell infiltrate was found.

Fifteen patients had an apical patch electrode present for 1 month to 2 years (mean 392 days). These patients had dense pericardial adhesions with an almost acellular connective tissue layer. As the pericardial changes matured, the pericardium adjacent to the apical patch electrode underwent remodeling with thinning and the eventual presence of a gross leathery, shiny surface on inspection.

In one patient whose apical patch electrode was placed extrapericardially, no pericarditis occurred. In the remaining patients, who had an intrapericardial apical patch, clinical manifestations of acute pericarditis were demonstrated postoperatively. However, none had clinical evidence of pericardial constriction.

Pitting or "thumbprints" are seen at the site of the patch electrode due to the corrugation of the lead surface, which helps to identify the pericardium as overlying the patch electrode. The pericardial changes were localized to the apical patch electrode (Fig. 1D).

Pathologic changes related to the intravascular electrodes (Table 2). Twenty-three of the 25 patients had the spring-patch electrode configuration; in two patients the patch-patch configuration was used because of high defibrillation thresholds at the time of defibrillator implantation (>25 J). In 4 (17%) of the 23 patients with a superior vena cava

Table 2. Pathologic Changes Associated With Intravascular Electrodes

	No. of Patients
SVC spring electrode	
Large thrombus	4
Asymptomatic emboli	
SVC thrombus associated	2
Not SVC thrombus associated	1
SVC "burn"	1
RV electrode (rate-sensing)	
Large thrombus	1

RV = right ventricle; SVC = superior vena cava.

spring electrode, a large intravascular thrombus was associated with the electrode. In two patients, multiple pulmonary emboli were demonstrated at autopsy; in both patients, no emboli were clinically suspected. In one patient, clinically recognized pulmonary emboli occurred with no evidence of an associated thrombus surrounding the superior vena cava electrode. Only one patient had an associated large thrombus in relation to the right ventricular (rate-sensing) electrode, without pulmonary emboli demonstrated at autopsy.

An electrical "burn" injury was noted in the superior vena cava of a patient who had a total of 59 defibrillations with the automatic implantable cardioverter-defibrillator. In this patient, regional vein wall destruction with associated thrombus was seen at autopsy (Fig. 2). The normal wall architecture was replaced with fibrous tissue with an adherent thrombus.

Pathologic changes related to the electrical injury (Table 3, Fig. 3). In all eight patients who received implanted leads only, no discernible histologic changes were seen in the epicardium or myocardium subjacent to the apical patch electrode. In seven patients who received one defibrillation during electrophysiologic testing but no additional defibrillations, no pathologic changes were observed. In two of five patients who received two to five shocks (mean 3.8), contraction band necrosis occurred. In one patient with eight defibrillations, vacuolar clearing changes were observed in myocytes subjacent to the apical patch electrode with loss of myocytes and fibrosis.

Four patients had 21 to 74 defibrillations (mean 45). In patients whose defibrillator discharged repeatedly within 24 hours of death, contraction band necrosis was observed subjacent to the patch electrode. In four patients, cytoplasmic vacuolar clearing was observed in the myocytes subjacent to the apical patch electrode with diffuse myocyte loss and fibrosis.

In the 15 hearts that were available for review, multiple sections were obtained through both the subepicardial area under the patch electrode and the unaffected myocardial sections away from the electrode. In all hearts thus examined, the visual estimate of the tissue demonstrating the pathologic changes did not exceed 2% of the left myocardial mass.

Discussion

Pericardial changes related to the apical patch electrode. Pericarditis is a nonspecific inflammatory response to pericardiotomy either as a consequence of the cardiac surgery or as a result of intrapericardial apical patch lead insertion. In our series, all the patients, except the one who had an extrapericardial lead, developed clinical manifesta-

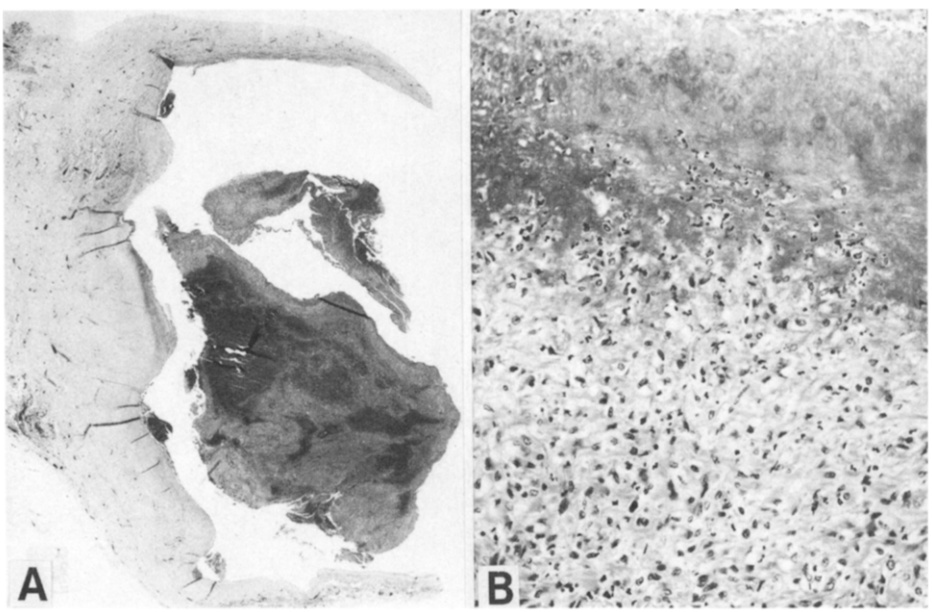


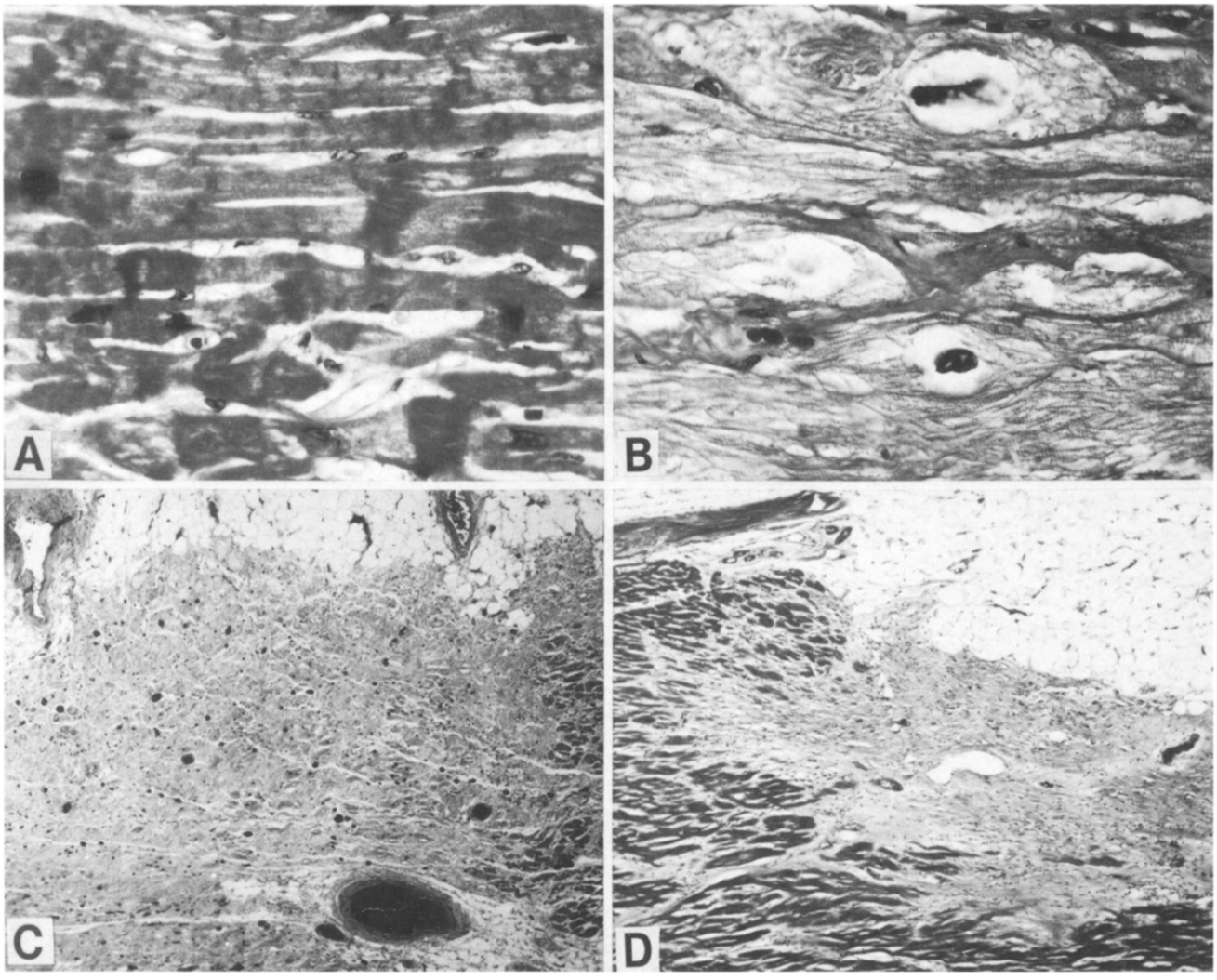
Figure 2. Superior vena cava changes. **A,** Superior vena cava with obstructive organizing thrombus. **B,** Wall of superior vena cava showing burn injury at the luminal margin **(top)** and inflammation and granulation tissue replacing the vessel wall **(below)** (Hematoxylin-eosin stain; original magnifications: **(A)** ×10, **(B)** ×200; both reduced by 30%.)

Table 3. Pathologic Changes Related to Electrical Injury Under the Apical Patch Electrode

No. of Patients	Defibrillations		Contraction Band Necrosis (subepicardial)	Vacuolar Cytoplasmic Clearing	Loss of Myocytes
	Total No.	No. <24 Hours Before Death			
8	0	0	Absent	Absent	Absent
7	1	0	Absent	Absent	Absent
5	2 to 5	1	2	Absent	Absent
1	8	0	Absent	1	1
4	21 to 74	4	2	4	4

tions of acute pericarditis postoperatively, manifested by a transient pericardial rub, fever and inspiratory pain. Those changes generally resolved within 48 to 72 hours. They were accompanied in some patients by echocardiographic signs of pericardial effusion but without evidence of tamponade. Pathologic changes varied from a thin fibrin layer deposition in the pericardial-epicardial interface within 24 hours of pericardiotomy and lead placement to progressive changes of organizing pericarditis. The early changes were generalized, becoming localized to the apical patch electrode and the surrounding tissue as the pericarditis matures. Early polymorphonuclear leukocyte infiltrate, which was seen in the first week, was replaced with a mononuclear

Figure 3. Myocardial changes beneath the patch in four patients. **A,** Contraction bands in myocytes. **B,** Clearing of myocyte cytoplasm. **C,** Subepicardial zone of cleared myocytes. **D,** Subepicardial replacement fibrosis. (Hematoxylin-eosin stain; original magnifications: **(A)** and **(B)** ×500 **(C)** and **(D)** ×50; all reduced by 25%.)



cell infiltrate at about 1 week. The pericardial changes progressed to a dense, connective tissue layer that underwent remodeling with disappearance of the cellular infiltrate and further deposition of collagen. Eventually, in patients whose apical patch electrode had been present for several months, a thin, leathery adhesion of parietal pericardium, the electrode and the visceral pericardium formed a compact, dense layer (Fig. 1).

Thromboembolic complications related to the intravascular leads. Thromboembolic phenomena have been reported in association with permanent transvenous pacing catheters in 0.6% of patients in one series (7) and 3 to 5% of patients of another series (8). In a more recent study (9), the incidence of asymptomatic pulmonary emboli, demonstrated on routine radionuclide lung scanning 2 weeks after pacemaker lead insertion, was 15%. The most common factor predisposing to thromboembolic events was congestive heart failure (10). The prevalence of this complication may be grossly underestimated, however, as documented by Stoney et al. (11), who demonstrated total occlusion of the deep venous system of the arm in 22% of 32 consecutive patients studied by venography a mean of 18 months after permanent pacemaker insertion. Severe, but partial obstruction with collateral circulation was noted in an additional 34%. Clinical signs suggesting thrombosis were unusual, however.

In our series, the incidence of large venous thrombi confirmed at autopsy was relatively high (20%) as was the incidence of asymptomatic emboli (8%). These findings at autopsy, however, are not strictly comparable with the clinical studies because most catheter-associated thrombi are clinically silent, as the study of Stoney et al. (11) suggests. The possible sources of pulmonary emboli include calf or leg veins, pelvic veins or intracardiac thrombi and the intravascular electrodes. Prolonged bed confinemant and immobility predispose to formation of venous thrombi. Nevertheless, the thrombi associated with the superior vena cava electrode cannot be excluded as a possible source of emboli in at least two of our patients. The superior vena cava lead has a larger profile (12F) and a larger surface area than those of a conventional pacemaker lead. This could increase stasis and thus predispose to thrombosis.

A possible alternative to using the superior vena cava lead includes implantation of two electrode patches at the time of surgery. This technique would offer an advantage in patients undergoing thoracotomy for another reason, for example, coronary artery bypass surgery, aneurysmectomy or valve replacement. It is not known whether such an approach would alter the morbidity of the procedure in patients who require only placement of an automatic implantable cardioverter-defibrillator. Thus, the possible risk of thrombosis should be balanced against an additional risk of thoracotomy in an otherwise compromised patient who typically has significant cardiac dysfunction.

Myocardial changes caused by electrical defibrillation. Effects of direct current cardioversion by external paddles or direct cardiac application have been studied by previous investigators. Transient elevations of cardiac creatine kinase, MB fraction (MB CK) have been documented (14). Warner et al. (4) described gross and histologic changes in 31 of 39 dogs that received 10 defibrillations with 400 J of energy each to the chest wall using 8 cm electrodes and in 12 dogs using 4 to 5 cm electrodes. The changes were confined to the subepicardial area and consisted of necrosis in the path of the current flow (between the paddles). Microscopic changes of increased granularity at 26 minutes, loss of striations in the subepicardial muscle at 3 days and fibrosis at 2 weeks were noted. Electron microscopy demonstrated mitochondrial vacuolization, disarray and fragmentation of myofibrils and electron-dense bodies in the degenerating mitochondria, thought to represent calcium accumulation. The authors suggested a possible role of calcium influx as the mechanism of the myocardial injury.

Van Vleet et al. (5) studied 18 normal dogs in which transthoracic shocks were delivered with a trapezoidal waveform defibrillator. Eleven dogs given one to six shocks at 1.2 to 1.9 A/kg per shock did not have cardiac changes at autopsy performed 2 hours after shock delivery. Of seven dogs given six suprathreshold shocks (3.2 to 10.6 A/kg), one dog died and four were found to have myocardial lesions. These lesions were apparent on gross inspection and consisted of discrete, pale areas located in the path of the electrodes. Microscopic and ultrastructural studies revealed 1) damage to the mitrochondrial membranes and sarcoplasmic reticulum, 2) intracellular edema and 3) contraction band change and nuclear pyknosis (5).

The energy delivery by the automatic defibrillator is considerably smaller than that used in the experimental animals in the previously mentioned studies. However, some of the histologic changes noted in the subepicardial layer subjacent to the patch electrode have similarities to the changes seen in the experimental animals in which cardioversion was used. These changes were not present in patients who had an apical patch lead and who received only a single internal defibrillation during the electrophysiologic study (Table 2). Thus, it is unlikely that the histologic changes observed in the subepicardial layer are related to the lead itself. Furthermore, the pathologic changes are the most marked in those patients who received the greatest number of internal defibrillations.

Causes of contraction band necrosis. Contraction band necrosis confined to the myocardium beneath the patch electrode was seen in patients who had internal defibrillations within 24 hours of death, but did not occur in two such patients and was also observed in one patient who had no internal defibrillations 24 hours before death. Thus, it is possible that this pathologic response may represent a nonspecific change related to a reflow injury (15). It is further

JACC Vol. 10, No. 2
August 1987:382–8

possible to speculate that the individual susceptibility to contraction band necrosis change is dependent on other local factors, such as presence of ischemia, changes in pH, presence of free radicals or some other factor as yet undetermined. Because the contraction band phenomenon was largely confined to the area beneath the patch in those patients receiving shocks in the immediate premortem interval (<24 hours before death), it seems more probable that it was secondary to electrical injury. Vacuolar cytoplasmic clearing may be due to mitochondrial damage, similar to the changes demonstrated by Warner (4) and Van Vleet (5) and their coworkers in the experimental animals. This change may lead to myocyte loss and subepicardial fibrosis.

Thus, the contraction band phenomenon may represent an early response to electrical injury which, after repeated defibrillations, may lead to cytoplasmic vacuolization and eventual cell necrosis, followed by fibrosis. The myocardial mass thus affected is small, and is estimated to be <2% of the total myocardial mass. The physiologic effects of the localized myocardial injury and fibrosis in the tissue subjacent to the apical patch electrode are unknown. It is theoretically possible that focal myocyte loss and scarring may lead to alteration in tissue properties and genesis of new foci of reentry and new ventricular arrhythmias.

Electrical injury that resulted in vein wall destruction was related to multiple defibrillations in one patient with the superior vena cava lead. Fibrous tissue and thrombus were present at the site of the wall injury, thus preventing bleeding and exsanguination in this patient.

Limitations of the study. Many patients received multiple external defibrillations both before implantation of the automatic implantable cardioverter-defibrillator and in the immediate 24 hour period before death. The exact number of external defibrillations is difficult to determine in any one patient because of incomplete documentation. However, the effects of the external defibrillations would be expected to produce generalized and random myocardial changes and would not necessarily be confined to the myocardium under the patch electrode. Thus, focal changes localized to the subepicardial layer immediately under the patch electrode are more likely to be the result of internal defibrillations due to the automatic implantable cardioverter-defibrillator.

Conclusion. The present study demonstrated, first, that pericarditis with focal changes related to the apical patch electrode is a universal finding of little clinical consequence. Early postoperative pericarditis results in progressive pericardial organization and remodeling related to the apical patch electrode. Constrictive pericarditis has not been demonstrated in any of the patients.

Second, the presence of a superior vena cava lead was associated with thrombi in 17% of the autopsy patients in our series. A right ventricular rate-sensing electrode appears to be less thrombogenic and was associated with thrombi in only 4% of patients. Although asymptomatic emboli were found in 8% of the autopsy patients, their possible origin includes leg veins, mural thrombi as well as the implanted leads. No patient died as a result of pulmonary emboli in this series.

Finally, multiple defibrillations are associated with recognizable localized pathologic changes subjacent to the apical patch electrode. They consist of contraction band necrosis, myocyte vacuolization and myocyte loss. These changes involve a small segment of myocardium immediately subjacent to the apical patch electrode. Multiple defibrillations may also occasionally produce vascular injury related to the intravascular superior vena cava lead.

Thus, the automatic defibrillator device and its lead system and multiple defibrillations lead to little myocardial or pericardial injury. The electrophysiologic consequences related to the localized myocyte injury and fibrosis in this group of patients are of unknown significance at present.

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