

## CARDIOVASCULAR MEDICINE

# Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis

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**Objectives:** To assess the efficacy of the administration of magnesium as a method for the prevention of postoperative atrial fibrillation (AF) and to evaluate its influence on hospital length of stay (LOS) and mortality.

**Methods:** Literature search and meta-analysis of the randomised control studies published since 1966.

**Results:** 20 randomised trials were identified, enrolling a total of 2490 patients. Study sample size varied between 20 and 400 patients. Magnesium administration decreased the proportion of patients developing postoperative AF from 28% in the control group to 18% in the treatment group (odds ratio 0.54, 95% confidence interval (CI) 0.38 to 0.75). Data on LOS were available from seven trials (1227 patients). Magnesium did not significantly affect LOS (weighted mean difference  $-0.07$  days of stay, 95% CI  $-0.66$  to 0.53). The overall mortality was low (0.7%) and was not affected by magnesium administration (odds ratio 1.22, 95% CI 0.39 to 3.77).

**Conclusion:** Magnesium administration is an effective prophylactic measure for the prevention of postoperative AF. It does not significantly alter LOS or in-hospital mortality.

Atrial fibrillation (AF) is a common complication after cardiac surgery. Most studies suggest that the frequency ranges between 25–40%.<sup>1–3</sup> Several reports have indicated that postoperative AF is associated with an increased length of stay (LOS) in hospital and consequently a greater utilisation of health care resources.<sup>4,5</sup> Postoperative AF is also associated with higher rates of postoperative stroke, compromised cardiac function, and adverse effects from drugs used to prevent AF.<sup>6,7</sup> Despite many years of clinical experience and a large amount of investigation, prevention and treatment of postoperative AF remain controversial. Many questions about the mechanisms and pathophysiology of AF remain unanswered,<sup>4</sup> further contributing to the ambiguity in reaching consensus about appropriate treatment. Increasing patient age is generally considered the greatest risk factor for postoperative AF and an aging population suggests that postoperative AF will continue to be a considerable problem in the future.<sup>1,8</sup>

Some studies have shown that serum hypomagnesaemia is common after coronary artery bypass grafts (CABG) and other types of cardiac surgery<sup>9–12</sup> and is associated with postoperative morbidity such as atrial tachyarrhythmia.<sup>10</sup> However, this has not been confirmed by all research.<sup>13</sup>

Some clinical trials have assessed the efficacy of magnesium as a method of intervention to reduce the incidence of postoperative AF. Often these studies were statistically underpowered and the results have been inconsistent.

We undertook a systematic review of the evidence from randomised controlled trials to assess the effectiveness of magnesium as a method for prevention of postoperative AF and to evaluate its influence on the incidence of postoperative stroke, mortality, and LOS.

## METHODS

### Search strategy

Titles and abstracts (where available) from Medline/PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) library database were searched from 1966 to July 2003. The search terms were "atrial fibrillation",

"atrial flutter", "surgery", and "magnesium". No language restrictions were applied. All references from papers obtained through the databases were searched by hand. References from papers obtained through the above procedure were searched for additional studies to be included.

Abstracts from the annual scientific meetings of the American College of Cardiology, American Heart Association, British Cardiac Society (*Heart*), European Society of Cardiology, and North American Society for Pacing and Electrophysiology between 2000 and 2003 were searched.

### Inclusion criteria for studies

Studies were included only if they met all of the following criteria:

- Randomised allocation of patients;
- placebo used as the control treatment
- well described protocol of magnesium administration as the intervention
- adequate data on treatment efficacy (supraventricular arrhythmia incidence)
- primary prevention of postoperative AF in CABG or valve surgery
- treatment started immediately preoperatively, perioperatively, or postoperatively;
- no confounding randomised drug treatment.

Double blind and non-blinded studies were included. Two investigators (EC, SM) evaluated the design of each trial for inclusion.

The primary outcome measure was the incidence of postoperative AF or atrial flutter except where total incidence of supraventricular arrhythmia was documented. Two other outcome measures, LOS and incidence of stroke, were also analysed when they could be obtained from the publication.

**Abbreviations:** AF, atrial fibrillation; CABG, coronary artery bypass graft; CENTRAL, Cochrane Central Register of Controlled Trials; CI, confidence interval; LOS, length of stay; OR, odds ratio

When the allocation of patients was not clear, the authors were approached. Two authors were contacted regarding the division of patients into control and treatment groups<sup>14 15</sup> but did not respond.

### Data collection and analysis

Two reviewers (MG, SM) independently extracted data into a collection table prepared for the study. All discrepancies between individually collected data were reviewed and resolved. Data collected were the number of patients, preoperative patient characteristics, preoperative medications, surgery specifications, type and route of intervention, incidence of AF or supraventricular tachyarrhythmia, LOS, stroke, and postoperative follow up.

### Statistical analysis

The occurrence of AF and stroke were treated as dichotomous variables and LOS was treated as a continuous variable. For comparison of LOS, the weighted mean difference was calculated as the difference between the mean values of LOS in treatment and control groups. Probability values of  $p < 0.05$  were considered significant.

Analysis was based on the intention to treat principle. Pooled effect estimates and heterogeneity between studies were analysed by the random effects model with the RevMan 4.1 statistical package (The Cochran Collaboration, Information Management System, www.cc-ims.net/RevMan).

## RESULTS

From the literature search and reference review, 20 studies that satisfied the inclusion criteria were found.<sup>16–33</sup> The publication dates spanned from 1982 to 2003.<sup>23 25</sup> Patient enrolment in single studies ranged from 20 to 400 patients.<sup>22 33</sup> The total number of randomised patients was 2490.

### Patient characteristics

Table 1 summarises patient characteristics. Eighteen studies included patients undergoing CABG surgery.<sup>16–22 24–31 33–35</sup> Four studies included at least some patients undergoing valve surgery,<sup>16 20 26 35</sup> but in each of these studies the majority of

patients enrolled underwent CABG procedures (range 88–100%) and only a minority underwent valve procedures (range 3–16%). One study included only patients undergoing valve surgery.<sup>23</sup> One study did not specify surgical procedure.<sup>32</sup> Aortic cross clamp time ranged from 38–103 minutes<sup>21 31</sup> in the control group and 35–91<sup>26 31</sup> minutes in the treatment group. Most of the studies excluded patients with abnormal renal function.<sup>16 18 19 21 24–27 30 31 33</sup> Some excluded patients with severely decreased left ventricular function<sup>16 19 21 27 29</sup> and thyroid<sup>19 29</sup> or respiratory disorders.<sup>16 19 21 25 27 30</sup>

Some studies also excluded patients taking  $\beta$  blockers, digoxin, calcium channel blockers, or diuretics preoperatively. In those trials that did not exclude patients being treated with preoperative  $\beta$  blockers, the proportion of patients being treated ranged from 26–85%.<sup>28 34</sup> For digoxin, the proportion of patients undergoing preoperative treatment ranged from 2–22%.<sup>20 31</sup> For calcium channel blockers, the proportion ranged from 15–89%.<sup>16 24</sup> For diuretics, the proportion ranged from 8–25%.<sup>24 31</sup>

### Detection and treatment

The majority of the trials used continuous ECG monitoring to detect arrhythmia.<sup>16–22 25–27 29 30 33 34</sup> Some of the studies used Holter recordings.<sup>24 31</sup> One study used a combination of continuous and Holter techniques.<sup>28</sup> For some, the method of detection was not specified.<sup>23 32 35</sup> The length of continuous ECG monitoring ranged from 24 to 120 hours.<sup>18 22 26 27</sup> The follow up period for arrhythmia detection was usually confined to hospital stay; however, in some trials there was a one month control visit.<sup>21</sup>

Regimens of magnesium administration varied and are summarised in table 2.

### Atrial fibrillation

Figure 1 presents the effect of magnesium on postoperative AF. Magnesium reduced the percentage of patients with AF from 28% in the control group to 18% in the treatment group (odds ratio (OR) 0.54, 95% confidence interval (CI) 0.38 to 0.75), with significant heterogeneity between trials ( $p < 0.001$ ).

**Table 1** Patient characteristics (control/treatment groups) of randomised controlled studies

Study	Number of participants	Mean age (years)	Men	Mean LVEF (%)	Previous MI	Blinding
Bert	60/63	64/63	83%/89%	49/48	NA	NS
Caspi	48/50	62/60	79%/68%	38/40	50%/54%	NS
Colquhoun	64/66	59/57	80%/83%	NA	53%/45%	DB
Dagdelen	55/93	61/63	78%/77%	NA	NA	DB
England	50/50	62/60	68%/58%	48/47	NA	DB
Fanning	50/49	62/59	78%/71%	49/50	42%/35%	DB
Forlani	50/54	64/64	88%/85%	55/52	66%/65%	NS
Harris	11/9	62/58	NA	50/55	NA	DB
Holden	37/33	45/47	32%/39%	NA	NA	DB
Jensen	28/29	61/61	100%/100%	NA	NA	DB
Kaplan	100/100	60/58	74%/76%	NA	58%/62%	NS
Karmy Jones	54/46	60/65	70%/61%	48/47	54%/50%	DB
Nurozler	25/25	54/56	92%/92%	66/67	28%/32%	DB
Parikka	71/69	54/57	82%/84%	59/61	NA	NS
Schwieger	100/100	61/61	64%/74%	NA	NA	NB
Shakerinia	25/25	65/67	68%/64%	65/67	72%/80%	NS
Toraman	100/100	61/62	83%/78%	NA	53%/49%	NS
Treggiari-Venzi	51/47	65/65	84%/89%	57/62	45%/38%	DB
Wollert	58/45	NA	NA	NA	NA	NS
Yeatman	200/200	63/64	78%/83%	NA	NA	DB

Blinding, method of blinding used in the study; DB, double blind study; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, data not available; NB, study not blinded; NS, blinding characteristics of study not specified.

**Table 2** Regimens of magnesium administration

Study	Infusion	Treatment initiation	Route	Treatment duration (hours)	Total amount (mmol)
Bert	Magnesium sulfate	Postop	iv	96	49
Caspi	Magnesium sulfate	Periop	iv	24	48
Colquhoun	Magnesium chloride	Postop	iv	48	50
Dagdelen	Magnesium sulfate	Preop	iv	144	37
England	Magnesium chloride	Periop	iv	Intraop	8
Fanning	Magnesium sulfate	Postop	iv	96	84
Forlani	Magnesium sulfate	Preop	iv	144	37
Harris	Magnesium chloride	Periop	iv	Intraop	16
Holden	Magnesium sulfate	Postop	im	72	7
Jensen	Magnesium sulfate	Postop	iv	96	110
Kaplan	Magnesium sulfate	Preop	iv	120	61
Karmy Jones	Magnesium sulfate	Postop	iv	24	58
Nurozler	Magnesium sulfate	Postop	iv	120	100
Parikka	Magnesium sulfate	Postop	iv	48	70
Schwieger	Magnesium sulfate	NA	iv	72	Supp
Shakerinia	Magnesium sulfate	Periop	iv	Intraop	NA
Toraman	Magnesium sulfate	Preop	iv	148	36
Treggiari-Venzi	Magnesium sulfate	Postop	iv	72	48
Wollert	Magnesium sulfate	Postop	iv	10	12
Yeatman	Magnesium sulfate	Periop	iv	Intraop	20

im, intramuscular; iv, intravenous; Periop, perioperatively; Postop, postoperatively; Preop, preoperatively; Supp, magnesium concentration <1 mmol/l were supplemented until >1 mmol/l was reached.

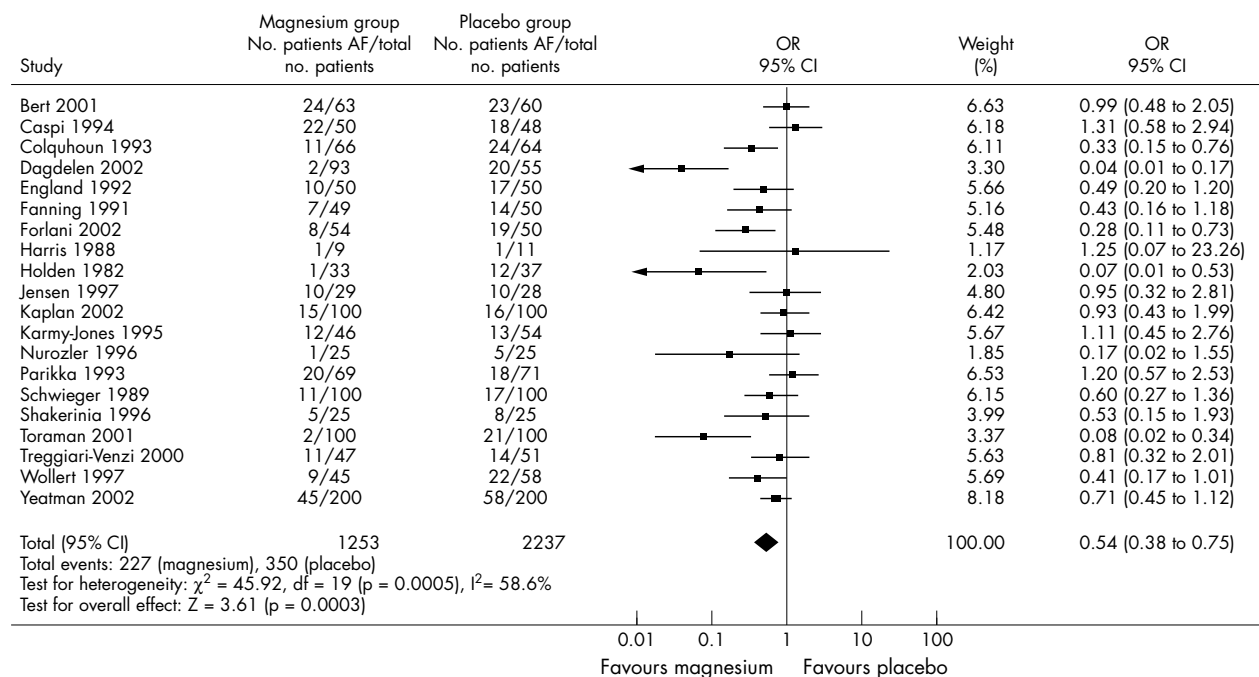
### Dosage

To assess whether this heterogeneity was related to the dose of magnesium administered, trials were subdivided into low (< 35 mmol), medium (35–50 mmol), and high (> 50 mmol) dosages of magnesium. In the five trials with low dose magnesium (693 patients), the percentage of patients with AF was reduced from 31% in the control group to 20% in the treatment group (OR 0.50, 95% CI 0.29 to 0.87). In the seven trials with medium dose magnesium (901 patients), the percentage of patients with AF was reduced from 32% in the control group to 17% in the treatment group (OR 0.36, 95% CI 0.16 to 0.82). In the six trials with high dose magnesium (646 patients), the percentage of patients with AF was reduced from 23% in the control

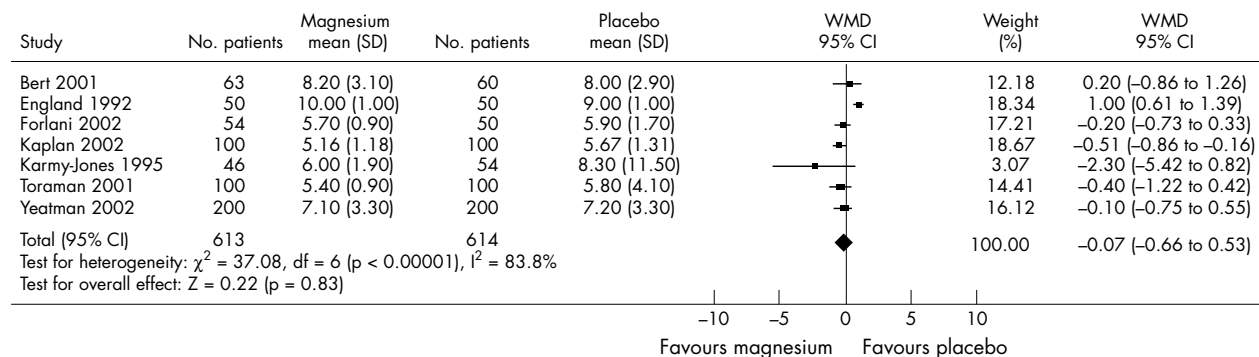
group to 20% in the treatment group (OR 0.87, 95% CI 0.59 to 1.29).

### Timing

To assess possible differences related to timing of magnesium administration, trials were subdivided into those with preoperative, perioperative, and postoperative regimens. In the four trials with preoperative magnesium administration (652 patients), the percentage of patients with AF was reduced from 25% in the control group to 8% in the treatment group (OR 0.19, 95% CI 0.05 to 0.76). In the five trials with perioperative magnesium administration (668 patients), the percentage of patients with AF was reduced from 31% in the control group to 25% in the treatment group (OR



**Figure 1** Incidence of postoperative atrial fibrillation. AF, atrial fibrillation developed postoperatively; CI, confidence interval; OR, odds ratio; total no. patients, total number of patients enrolled in the study.



**Figure 2** Effects of magnesium on hospital length of stay (days). WMD, weighted mean difference.

0.74, 95% CI 0.53 to 1.05). In the 10 trials with postoperative magnesium administration (970 patients), the percentage of patients with AF was reduced from 31% in the control group to 22% in the treatment group (OR 0.63, 95% CI 0.41 to 0.96).

### Surgery type

To assess possible differences related to the type of surgery, trials were subdivided into those with patients undergoing CABG surgery only, CABG and valve surgery, and valve surgery only. In the 14 trials with CABG surgery only (1794 patients), the percentage of patients with AF was reduced from 28% in the control group to 17% in the treatment group (OR 0.51, 95% CI 0.32 to 0.79). In the four trials with CABG and valve surgery (523 patients), the percentage of patients with AF was reduced from 26% in the control group to 22% in the treatment group (OR 0.77, 95% CI 0.51 to 1.16). Only one study had valve surgery alone (70 patients), in which the percentage of patients with AF was reduced from 32% to 3% (OR 0.07, 95% CI 0.01 to 0.53).

### LOS and mortality

Seven trials reported the effect on LOS with a total of 1227 patients (fig 2). Magnesium did not significantly reduce LOS (weighted mean difference  $-0.07$ , 95% CI  $-0.66$  to  $0.53$ ). No data were available on hospitalisation costs. Twelve trials reported data on postoperative mortality, with a total of 1471 patients. Overall mortality was 0.7% and was not significantly affected by magnesium (OR 1.22, 95% CI 0.39 to 3.77).

## DISCUSSION

### Main results

This meta-analysis showed that magnesium administration significantly reduced the frequency of postoperative AF. Preoperative administration of magnesium was more effective in prevention of postoperative AF than intraoperative or postoperative prevention. Mortality and LOS were not affected significantly.

### Comparison with other prophylactic interventions

A previous meta-analysis evaluated  $\beta$  blockers, sotalol, amiodarone, and pacing as methods of prevention of postoperative AF.<sup>36</sup> All these interventions reduced postoperative AF significantly:  $\beta$  blockers with OR of 0.39 (95% CI 0.28 to 0.52); sotalol with OR of 0.35 (95% CI 0.26 to 0.49); amiodarone with OR of 0.48 (95% CI 0.37 to 0.61); and biatrial pacing with OR of 0.46 (95% CI 0.30 to 0.71). Our results suggest that magnesium is roughly as effective as most of the common prophylactic interventions in reducing postoperative AF, with OR in the similar range.

### Adverse effects

One problem with the use of antiarrhythmic agents to prevent postoperative AF is that the majority of patients do not develop postoperative AF after cardiac surgery but would still be exposed to possible side effects of prophylactic intervention. Routine prophylaxis of postoperative AF is estimated to expose 80% of patients to drugs for which there is no actual need.<sup>37</sup> Intravenous magnesium is appealing because it avoids most of the proarrhythmic risks associated with other drugs. In general, few risks are associated with the prevention of hypomagnesaemia when renal function is normal.<sup>38</sup>

### Mechanism of action

The mechanisms by which magnesium administration reduces the incidence of postoperative AF are not entirely known. Depletion of magnesium, as shown in some studies of cardiac surgery patients, may be proarrhythmic.<sup>39-41</sup> At the same time, administration of magnesium significantly increases atrial refractoriness.<sup>42-43</sup> The combination of the treatment effects of correcting magnesium depletion and of increasing atrial refractoriness caused by magnesium administration is probably responsible for the overall beneficial effect of magnesium.

### Heterogeneity

There was significant heterogeneity among the trials, attributable to a number of factors such as different exclusionary criteria, various arrhythmia monitoring techniques, diverse definitions of AF, the surgical procedure performed, and alternative administration regimens and dosages of magnesium. Subdivision of the trials by times of initiation showed that preoperative administration was most effective in reducing postoperative AF. Hypomagnesaemia can occur before cardiac surgery in some patients<sup>10-12</sup> and so this provides a possible explanation for the increased effectiveness of preoperative administration. Subdivision of the trials by the total amount of magnesium administered showed that a low dose of magnesium was most effective in reducing postoperative AF. Other individual studies have shown that a high dose of magnesium was significantly more effective than a low dose in preventing AF.<sup>44</sup> Subdivision of the trials by surgery type showed that magnesium was more effective in trials with CABG surgery alone than when CABG was combined with valve surgery. Magnesium appeared to be most effective in the single trial in which only valve operations were performed. Factors such as length of treatment may have confounded the analyses, so the above conclusions should be treated cautiously.

## LOS and mortality

Postoperative AF has been associated with LOS extended by three to four days<sup>7</sup> and accompanying increases in hospital costs.<sup>44-45</sup> Magnesium did not significantly reduce the LOS in this meta-analysis. Fewer than half of patients will develop postoperative AF and still fewer develop prolonged AF, so the effect of magnesium on LOS in patients prone to AF would have to be very large to be able to detect an effect of LOS in the total population. It is possible that postoperative AF is a confounding variable and not necessarily the cause of the associated adverse events. Since only seven studies provided data on LOS, additional studies or data are warranted. Likewise, because mortality rates after cardiac surgery are very low, no trial of sufficient statistical power can realistically be done. Only two trials reported data on postoperative stroke.<sup>30-33</sup> Therefore, the effect of magnesium on postoperative stroke could not be determined.

## Limitations

This meta-analysis is limited by the lack of complete availability of relevant data, particularly for LOS, stroke, and mortality. The studies we analysed span over 20 years during which time there was an intensive evolution of cardiac surgery techniques. Nevertheless, treatment benefit seemed to be similar over time. Some studies excluded groups of high risk but commonly encountered cardiac patients. This limits the extrapolation of the data from the clinical trials into everyday practice. Lastly, even though an examination search was done, meta-analysis itself is associated with a publication bias in that studies with a positive result are more likely to be published than negative studies.

## Conclusion

Magnesium administration is effective for reducing postoperative AF, with a magnitude of the effect comparable with that of proposed antiarrhythmic drugs. Magnesium administration did not significantly reduce hospital LOS or mortality. Questions remain about the optimal regimen of administration and its efficacy in combination with other drugs.

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## IMAGES IN CARDIOLOGY

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### Apical left ventricular aneurysm presenting with malignant ventricular tachycardia responsive to aneurysmectomy

A 76 year old man with no prior cardiac history was admitted after three episodes of syncope. With symptoms, telemetry revealed a rapid monomorphic rhythm (panel A) consistent with ventricular tachycardia (VT). ECG and cardiac markers were unremarkable. Echocardiography revealed an apical defect emptying into a large thin-walled chamber (panels B, C, D). Doppler interrogation revealed bidirectional flow between the left ventricle (LV) and this chamber, consistent with true aneurysm of the LV apex versus contained rupture of the LV apex with pseudoaneurysm formation. Cardiac catheterisation showed a 40% plaque in the mid left anterior descending coronary artery. At cardiac surgery, the abnormality was resected and the LV repaired with a pericardial patch. Recovery was uneventful with no further VT on telemetry and no VT inducible at electrophysiology study. Pathological examination of the resected tissue revealed true aneurysm with surviving myocytes scattered throughout areas of scar. Aetiology was likely an old myocardial

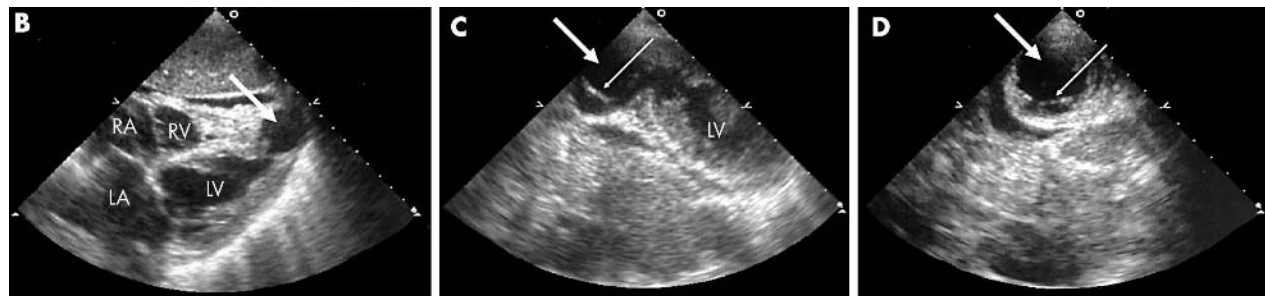
infarction, caused by left anterior descending coronary artery thrombosis or spasm at the site of a focal and intrinsically non-obstructive plaque.

Differentiation of true aneurysm from pseudoaneurysm by echocardiography can be difficult. Here, true aneurysm was indicated by the presence of continuous endomyocardial and pericardial layers extending from the normal portion of the left ventricle throughout the aneurysmal sac. Aneurysms of the left ventricle, often associated with ventricular arrhythmias, typically form by dilation of infarct or infarct scars, although congenital and inflammatory aneurysms have been described. Resection of the aneurysm and surrounding abnormal myocardium can cure the ventricular arrhythmias, as in this case.

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Telemetry strip of leads I and V1 demonstrating the spontaneous onset of monomorphic ventricular tachycardia with a right bundle branch block pattern at approximately 280 beats/min.



Subcostal (B) and off-axis apical (C) views from transthoracic echocardiogram demonstrating left ventricular apical defect. Panel D is another apical view showing a cross section of the aneurysmal sac. Heavy arrows indicate an echo-free chamber communicating with the left ventricular cavity by an orifice with a narrow neck. Here, the definitive feature distinguishing true aneurysm from pseudoaneurysm is the presence of an endomyocardial border lining the cavity, as well as a continuous pericardial layer. Thin arrows indicate the residual myocardial layer in the wall of the aneurysmal chamber. Other findings that have been described to help distinguish between these two entities are the ratio of the maximal diameter of the neck to maximal diameter of the cavity (0.25 and 0.5 for pseudoaneurysm and 0.9 to 1 for aneurysm), and the flow characteristics of the chamber (turbulent flow by pulse Doppler in neck or within cavity in the pseudoaneurysm), which were not helpful in this case. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.