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Causes and prognosis of symptomatic pericardial effusions treated by pericardiocentesis in an Asian academic medical centre

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ABSTRACT

Introduction: This study aimed to investigate the causes, clinical management and outcomes of clinically significant pericardial effusions, and evaluate the practice of pericardiocentesis within an academic medical centre in Singapore, a multiethnic country in Southeast Asia.

Methods: Consecutive patients undergoing pericardiocentesis at a single Asian academic medical centre were identified. Patient demographics, echocardiographic findings, investigations, pericardiocentesis procedural details and clinical progress were tracked using a comprehensive electronic medical records system.

Results: Of 149 patients who underwent pericardiocentesis, malignancy (46.3%) followed by iatrogenic postsurgical complications (17.6%) were the most common causes of pericardial effusions. 77.3% of effusions were large and 69.8% demonstrated tamponade physiology. Pericardiocentesis guided by echocardiography and fluoroscopy was successful in 98.7% of patients and had a complication rate of 2.1%. Likelihood of effusion recurrence and survival-to-discharge was determined by the aetiology of the pericardial effusion. 24.6% of malignant effusions recurred and survival rates 12 months after drainage of a malignant pericardial effusion was 45.0%. Short-term mortality was highest among patients presenting with tamponade due to acute aortic syndromes and myocardial rupture due to ischaemic heart disease.

Conclusion: Cancer and iatrogenic complications were the most common causes of pericardial effusion in this large cohort of Singapore patients. Pericardiocentesis has a high success rate and relatively low complication rate. Prognosis and clinical course after pericardiocentesis is determined by the underlying cause of pericardial effusion.

Keywords: pericardial effusion, pericardiocentesis, tamponade

INTRODUCTION

Pericardial effusions are caused by a wide range of conditions and the distribution of these causes can vary globally. When complicated by tamponade, pericardiocentesis is potentially a life-saving intervention. There is limited data on patients with clinically significant pericardial effusions in Asia. The objectives of this study were to: (a) investigate the causes, clinical management and outcomes of clinically significant pericardial effusions; and (b) evaluate the practice of pericardiocentesis within an academic medical centre in Singapore, which is a multiethnic country in Southeast Asia.

METHODS

Consecutive patients undergoing pericardiocentesis at National University Heart Centre, Singapore (NUHCS) between August 2011 and February 2017 were identified from a comprehensive cardiac procedural database. Patient demographics, echocardiographic findings, investigations, pericardiocentesis procedural details and clinical progress were tracked using a comprehensive electronic medical records system. National University Hospital (NUH) is a 1,250-bedded academic medical centre in Singapore and provides tertiary services in oncology (National University Cancer Institute, Singapore) and cardiovascular medicine (NUHCS).

Echocardiographic findings of note that were recorded included ejection fraction, size of the pericardial effusion and the presence of tamponade physiology. The size of effusion was assessed semiquantitatively as mild (< 10 mm), moderate (10–20 mm) and large (> 20 mm) according to the measure of the largest echo-free space when viewed from the standard transthoracic echocardiographic windows.[(1)] The presence of tamponade was assessed holistically using a range of indicators that included diastolic right heart collapse, abnormal

ventricular septal motion, exaggerated inspiratory variability in mitral inflow velocity and inferior vena cava plethora.

Pericardiocentesis was guided either by using echocardiography alone or combined with fluoroscopy in the cardiac catheterisation laboratory upon the operator's discretion. Echocardiographic guidance was used to identify the largest collection of the pericardial effusion that was closest to the skin surface without intervening lung or liver tissue. Images were acquired from both the apical and subcostal regions to identify the safest approach. The pericardiocentesis needle was then introduced according to the inclination of the echo probe to the expected depth where the effusion was seen. Occasionally, the needle tip was visualised by the echocardiography probe to confirm entry into the pericardial space, although this was not consistently demonstrated (Fig. 1). Echocardiographic presence of the guidewire within the pericardial cavity was confirmed prior to insertion of the dilator. To further ensure correct placement of the sheath, agitated saline (bubble contrast) was injected through the smallest dilator to confirm presence of bubbles in the pericardial space before further dilatation was performed. For patients undergoing fluoroscopy-guided pericardiocentesis, fluoroscopy in the cardiac catherisation laboratory was used to localise the advancing needle in relation to the cardiac silhouette, combined with contrast injection to determine entry into the pericardial space and to verify the pericardial location of the guidewire by visualising it coiling around the pericardial sac (Fig. 2). It was left to the operator's discretion whether echocardiography was used to complement the fluoroscopic images. The pericardial fluid underwent cytological, microbiological, microscopic and biochemical analyses, the latter consisting of glucose, protein and lactate dehydrogenase levels. Procedural details during pericardiocentesis that were recorded included site of needle entry (apical vs. subcostal), amount drained, occurrence of any complications and analysis of the pericardial fluid obtained. Causes of pericardial effusion were established based on clinical reasoning and the results of the pericardial fluid analysis.

Clinical progress, specifically recurrence of the effusion, need for repeated drainage and survival-to-discharge were recorded.

Patients were considered to have active cancer if the disease was diagnosed and treated within the past 12 months and the patient was in remission for less than 12 months. Patients were considered to have previously treated cancer if they were in remission for more than 12 months.

Continuous data was expressed as mean ± standard deviation. Continuous and categorical variables were assessed with unpaired *t*-test and Fisher's exact test, respectively. GraphPad Prism version 7.0 (GraphPad Software Inc, San Diego, CA, USA) was used for all statistical analyses. The study received institutional ethics approval from the National Healthcare Group Domain Specific Review Board, Singapore (approval no. 2017/00535).

RESULTS

From August 2011 to February 2017, 149 patients with a mean age of 64.5 ± 15.7 years underwent pericardiocentesis (Table I). Mean follow-up duration was 10.8 ± 13.2 months. 44.3% of patients were diagnosed with active cancer, and 6.0% of patients were considered to be in remission for over one year for previously treated cancer. More than half of cancers originated from the lung. Other common comorbidities included hypertension, hyperlipidaemia and coronary artery disease in 49.7%, 43.6% and 26.2% of patients, respectively. The most common presenting symptom was dyspnoea, reported by 51.0% of patients.

Table I. Patient demographics (n = 149).

Variable	**No. (%)**
Age (yr)*	64.5 ± 15.7
Male gender	81 (54.4)
Active cancer	66 (44.3)
Lung	37 (56.1)
Leukaemia/lymphoma	12 (18.2)
Breast	6 (9.1)

Gastrointestinal	3 (4.5)
Head and neck	3 (4.5)
Gynaecological	2 (3.0)
Other	3 (4.5)
Previously treated cancer	9 (6.0)
Coronary artery disease	39 (26.2)
Heart failure	21 (14.1)
Hypertension	74 (49.7)
Hyperlipidaemia	65 (43.6)
Myocarditis	8 (5.4)
Diabetes mellitus	23 (15.4)
End-stage renal failure	19 (12.8)
Chronic lung disease	10 (6.7)
Liver cirrhosis	7 (4.7)
Prior tuberculosis	8 (5.4)
Presenting symptoms	
Breathlessness/dyspnoea	76 (51.0)
Chest pain	30 (20.1)
Hypotension	30 (20.1)
Palpitation	13 (8.7)

**Data presented as mean ± standard deviation.*

81.7% of patients had left ventricular ejection function within normal limits and 77.3% of pericardial effusions were large in size (Table II). Tamponade physiology was present in nearly 70% of patients. In the remaining patients, pericardiocentesis was performed for diagnostic purposes or symptom relief. Loculated effusions were seen in four out of nine patients who had developed effusions after cardiac surgery.

Table II. Echocardiographic characteristics.

Variable	**%**
Left ventricular ejection fraction	
Normal (≥ 55%)	81.7
Impaired (< 55%)	18.3
Size of pericardial effusion	
Small	7.1
Moderate	15.6
Large	77.3
Tamponade physiology	
No	25.2
Yes	69.8

Procedural success was achieved in all but one patient, and a mean 520 ± 408 mL of fluid was drained during the index procedure (Table III). Subcostal approach was used in 47.7% of patients, and only 31.5% of patients were guided by both echocardiography and fluoroscopy. There were 3 (2.0%) serious complications, all of which required surgical interventions – two patients with right ventricular punctures (both using subcostal approach; one using echocardiographic guidance alone, and the other with both echocardiographic and fluoroscopic guidance) and one patient with left ventricular puncture (using an apical approach and echocardiographic guidance). All three patients survived to hospital discharge. In two patients, self-terminating atrial tachyarrhythmias occurred, which did not require any interventions.

Table III. Procedural details.

Variable	**No. (%)**		
	All (n = 149)	**Echocardiography guided (n = 102)**	**Echocardiography and fluoroscopy guided (n = 47)**
Acute procedural success (%)	148 (99.3)	101 (99.0)	47 (100.0)
Amount drained (mL)[*,†]	520 ± 408	517 ± 341	507 ± 506
Site of entry			
Apical	78 (52.3)	58 (56.9)	20 (42.6)
Subcostal	71 (47.7)	44 (43.1)	27 (57.4)
Complications requiring intervention	3 (2.0)	2 (2.0)*	1 (2.1)[‡]

**Data presented as mean ± standard deviation. †One patient with right ventricular puncture and one patient with left ventricular puncture. ‡One patient with right ventricular puncture.*

76.9% of pericardial effusions were bloodstained, while the remainder was described as yellow or serous in appearance. No mycobacterial infection was found in our cohort. Out of 69 patients with malignant pericardial effusions, for only 31 (44.9%) patients were abnormal cytology reported. On comparing pericardial fluid from malignant effusions (which would be expected to be exudative) against those due to heart failure and uraemia (which would be expected to be transudative), there were no differences in cell counts and protein levels.

However, malignant pericardial effusions had lower glucose levels (malignant effusion: 4.0 ± 2.4 mmol/L; heart failure effusion: 7.0 ± 5.0 mmol/L; $p < 0.01$) and higher lactate dehydrogenase levels (malignant effusion: 3,181 ± 3,879 IU/L; heart failure effusion: 649 ± 501 IU/L; $p < 0.01$). There was significant overlap in both glucose and lactate dehydrogenase levels between the two groups.

The most common cause of pericardial effusion was due to malignancy, followed by iatrogenic complications of cardiovascular interventions (17.4%; Table IV). In the latter, five patients were diagnosed following catheter ablation procedures for arrhythmias, four patients after percutaneous coronary arterial interventions, two patients post myocardial biopsy and the remaining 15 patients after cardiac surgery. Recurrences (24.6%) were observed most frequently in patients with malignant effusions, but repeat drainage was performed in only six out of 17 patients. One patient underwent surgery to create a pericardial window. Survival-to-discharge was closely related to the aetiology, with the lowest survival rates seen among patients with acute ascending aortic syndrome (aortic dissections or rupture of ascending aortic aneurysms) and ventricular free wall rupture following acute myocardial infarctions. In contrast, all patients diagnosed with pericarditis, uraemia, heart failure and autoimmune causes survived to discharge. Survival rate at 12 months after pericardiocentesis for malignancy effusions was 45.0%.

Table IV. Causes of pericardial effusion, likelihood of recurrence and survival-to-hospital discharge.

Variable	**No. (%)**		
	Incidence	**Recurrence**	**Survival-to-discharge**
Malignancy	69 (46.3)	17 (24.6)	50 (72.5)
Postsurgical complications	26 (17.4)	1 (3.8)	20 (76.9)
Effusion associated with pneumonia	11 (7.4)	2 (18.1)	8 (72.7)
Pericarditis	9 (6.0)	2 (22.2)	9 (100)
Uraemia	7 (4.7)	1 (14.3)	7 (100.0)
Acute ascending aortic syndrome	7 (4.7)	0 (0)	3 (42.9)
Heart failure	6 (4.0)	0 (0)	6 (100.0)

Multisystemic autoimmune disease	5 (3.4)	1 (20.0)	5 (100.0)
Idiopathic	3 (2.0)	0 (0)	3 (100.0)
Dressler's syndrome	3 (2.0)	0 (0)	3 (100.0)
Myocardial rupture	2 (1.3)	0 (0)	0 (0)
Over-anticoagulation	1 (0.7)	0 (0)	0 (0)
Overall (n = 149)	149 (100.0)	24 (16.1)	114 (76.5)

DISCUSSION

In our series of 149 patients undergoing pericardiocentesis, malignancy followed by iatrogenic postsurgical complications were the most common causes of pericardial effusions. Pericardiocentesis guided by echocardiography and fluoroscopy has a high success rate and relatively low complication rate. However, serious complications requiring surgical interventions may occur. Investigations routinely ordered for analysis of pericardial fluids have limited sensitivity. Effusion recurrence and survival after pericardiocentesis is determined by the aetiology of the pericardial effusion.

Causes of pericardial effusion vary depending on the geographical location of the survey. In less developed countries such as South Africa, infectious causes, such as tuberculosis, predominate.[2] Conversely, in advanced countries, complications of cardiac surgery and cancer are the most common causes.[3-5] Furthermore, the proportions of pericardial effusions caused by malignancy and postsurgical complications may be increasing over time, in part due to improved survival among cancer patients and increasing number of cardiac interventions in developed countries.[6]

The prognosis of pericardial effusion is essentially related to its aetiology.[1,7] Consistent with other series, patients with malignant pericardial effusions have poor prognosis with typical median survival of 3–7 months.[3-5,7] This is consistent with a 45.0% survival rate at 12 months in our patients. However, patients presenting with haemopericardium due to acute ascending aortic syndrome, which namely consists of aortic dissections or rupture of aortic

aneurysms, and free wall myocardial rupture had the worst short-term prognosis despite undergoing emergent surgery.

Our major complications rate of 2.0% was consistent with other large series, confirming the relative safety of pericardiocentesis.[4,8] Given the low incidence of complications, it was not possible to discern whether the site of pericardial access or the additional use of fluoroscopy for guidance impacted upon complication rates. However, while complications are uncommon, three patients with incidental ventricular puncture required surgical repair in our series. This observation should be a cautionary note about performing non-emergent pericardiocentesis in hospitals without cardiothoracic surgical support.

While pericardial fluid is routinely sent for cell count, measurements of glucose, protein, lactate dehydrogenase levels, cytology and microbiological analyses, diagnostic yields are limited. All tests listed above, except cytology, generally lack specificity, with significant overlap between transudative and exudative effusions.[9-11] Conversely, cytological analyses have lower sensitivity – in this study, only 44.9% – but 100% specificity. The positive diagnostic yield of 44.9% from cytological analysis of malignant pericardial effusion in our study was consistent with the rate of 40%–50% in the literature.[5] Interpreting analyses of pericardial fluid are also limited by firstly, the fact that most causes of pericardial effusion would be expected to produce an exudative, typically bloodstained effusion (76.9% in this series) and secondly, that the biochemical composition of physiological pericardial fluid differs from plasma serum.[12] In a recent study, physiological pericardial fluid from 30 patients undergoing elective coronary artery bypass grafting, but without a history of pericardial disease, was collected. Surprisingly, pericardial lactate dehydrogenase levels were on average 2.4 times higher than serum levels while protein levels were only 60% of serum levels.[12] There was also predominant lymphocytosis, which was 5.3 times higher than paired serum levels. This has led to several groups suggesting that analysis of pericardial biochemistry may be

unhelpful or have almost no diagnostic value in the contemporary management of pericardial effusions.[10,13]

Our study was limited by its retrospective design, lack of a systematic protocol for pericardiocentesis and advanced investigations of the pericardial fluid. However, the findings reflect real-world practices and are informative for future improvements in clinical care. Our results may have been biased due to the presence of tertiary cancer and cardiovascular surgical services within our institution due to which higher proportions of patients with malignant and postsurgical effusions would be referred for pericardiocentesis.

In conclusion, cancer and iatrogenic complications are the most common causes of pericardial effusion in this large cohort of Singapore patients. Pericardiocentesis has a high success rate and relatively low complication rate. Prognosis and clinical course after pericardiocentesis is determined by the underlying cause of pericardial effusion.

REFERENCES

1. Adler Y, Charron P, Imazio M, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). Endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015; 36:2921-64.
2. Reuter H, Burgess LJ, Doubell AF. Epidemiology of pericardial effusions at a large academic hospital in South Africa. Epidemiol Infect 2005; 133:393-9.
3. Lindenberger M, Kjellberg M, Karlsson E, Wranne B. Pericardiocentesis guided by 2-D echocardiography: the method of choice for treatment of pericardial effusion. J Intern Med 2003; 253:411-7.

4. Akyuz S, Zengin A, Arugaslan E, et al. Echo-guided pericardiocentesis in patients with clinically significant pericardial effusion. Outcomes over a 10-year period. Herz 2015; 40 Suppl 2:153-9.
5. Sánchez-Enrique C, Nuñez-Gil IJ, Viana-Tejedor A, et al. Cause and long-term outcome of cardiac tamponade. Am J Cardiol 2016; 117:664-9.
6. Ma W, Liu J, Zeng Y, et al. Causes of moderate to large pericardial effusion requiring pericardiocentesis in 140 Han Chinese patients. Herz 2012; 37:183-7.
7. Kil UH, Jung HO, Koh YS, et al. Prognosis of large, symptomatic pericardial effusion treated by echo-guided percutaneous pericardiocentesis. Clin Cardiol 2008; 31:531-7.
8. Tsang TS, Barnes ME, Hayes SN, et al. Clinical and echocardiographic characteristics of significant pericardial effusions following cardiothoracic surgery and outcomes of echo-guided pericardiocentesis for management: Mayo Clinic experience, 1979-1998. Chest 1999; 116:322-31.
9. Meyers DG, Meyers RE, Prendergast TW. The usefulness of diagnostic tests on pericardial fluid. Chest 1997; 111:1213-21.
10. Ben-Horin S, Bank I, Shinfeld A, et al. Diagnostic value of the biochemical composition of pericardial effusions in patients undergoing pericardiocentesis. Am J Cardiol 2007; 99:1294-7.
11. Karatolios K, Pankuweit S, Maisch B. Diagnostic value of biochemical biomarkers in malignant and non-malignant pericardial effusion. Heart Fail Rev 2013; 18:337-44.
12. Ben-Horin S, Shinfeld A, Kachel E, Chetrit A, Livneh A. The composition of normal pericardial fluid and its implications for diagnosing pericardial effusions. Am J Med 2005; 118:636-40.

13. Akyuz S, Arugaslan E, Zengin A, et al. Differentiation between transudate and exudate in pericardial effusion has almost no diagnostic value in contemporary medicine. Clin Lab 2015; 61:957-63.

FIGURES

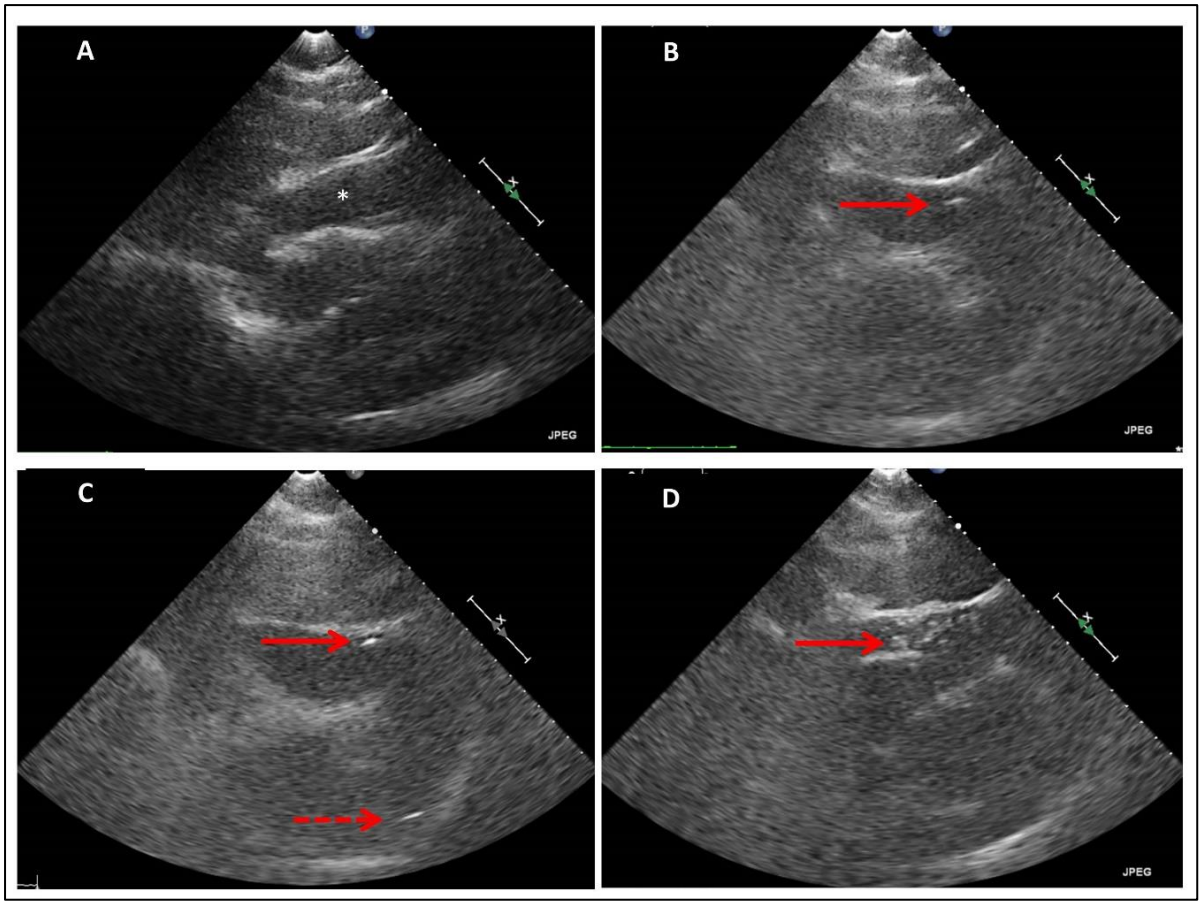

Fig. 1 Echocardiograms of echocardiography-assisted pericardiocentesis show (a) subcostal view of a large pericardial effusion (*) with diastolic collapse of the right heart; (b) visualisation of the needle tip (arrow) entering the pericardial space; (c) presence of the needle (solid arrow) and guidewire (broken arrow) within the pericardial space; and (d) presence of echocardiographic bubbles in the pericardial space after injection of agitated saline (arrow) via a dilator.

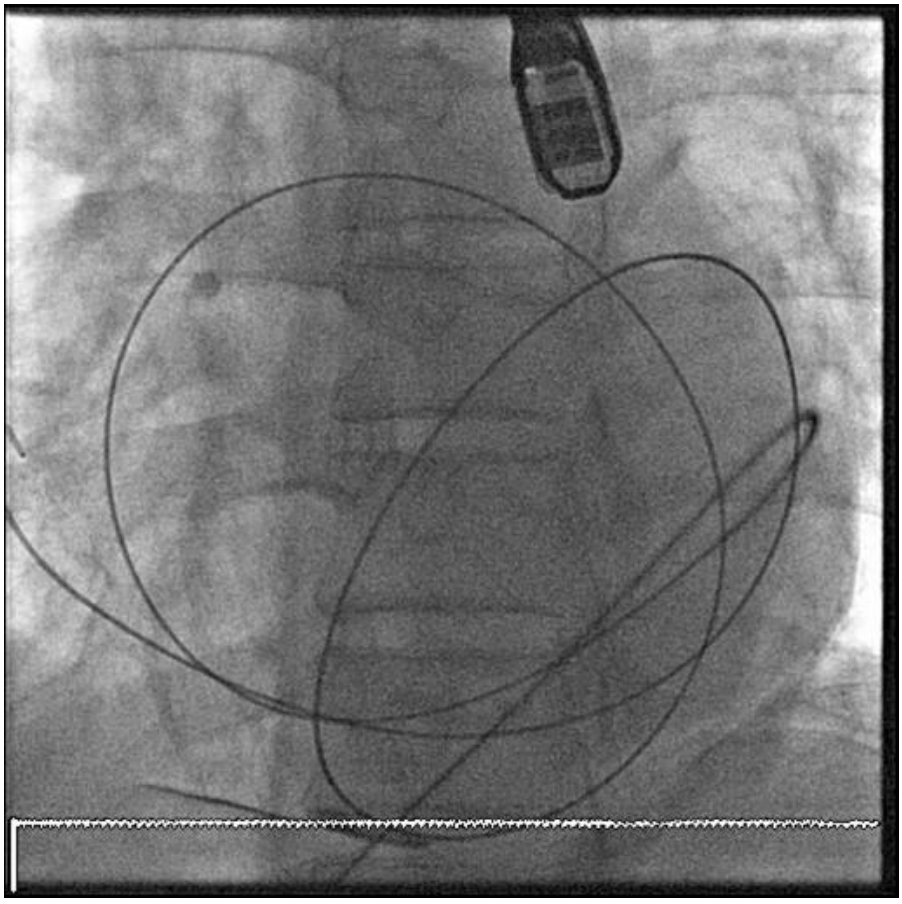

Fig. 2 Fluoroscopy-guided pericardiocentesis. Note the use of small amounts of contrast to track the progress of the needle from the site of puncture into the pericardial cavity. The position of the guidewire within the pericardial space was confirmed by the passage of the guidewire going around the pericardial sac and traversing multiple anatomical planes, which would not have been possible if the guidewire was within the heart.