Ultrasound guided percutaneous thrombin injection for the treatment of iatrogenic pseudoaneurysms

Editor—Elford and colleagues recently described rapid and spectacular thrombotic occlusion of an iatrogenic axillary artery pseudoaneurysm following injection of thrombin.1 The authors concluded that this treatment is “safe” and that it should be considered as the treatment of choice for iatrogenic pseudoaneurysm. Although we agree that thrombin injection is promising, there are important safety issues to address before this treatment can be adopted routinely.

There are little safety data on the immunological effects of these products. Fibrinogen1 thrombin products are widely used to help achieve haemostasis during complex cardiac surgery. A recent study of 21 patients undergoing cardiothoracic surgery with fibrin glue (bovine fibrinogen clotted with bovine thrombin) demonstrated IgM and IgG antibodies to bovine thrombin, fibrinogen and factor V in every patient.2 Although there were no bleeding complications reported in this study, these antibodies can cross-react with their human counterparts and result in severe haemorrhagic complications.3 Antibodies have also been detected after administration of topical bovine thrombin during dental procedures.4 As direct intravascular injection may cause areas of localised thrombosis and haemostatic response, caution appears to be appropriate until immunologically compatible human thrombin is routinely available.

Many pseudoaneurysms occur after coronary interventional procedures and optimal timing of thrombin treatment has yet to be determined. Thrombotic complications following administration of intravascular bovine thrombin have been described5 which may have resulted from leakage of thrombin from the pseudoaneurysm into the systemic circulation, although other mechanisms are also possible.6 Circulating thrombin should rapidly be diluted or neutralised by thrombomodulin and antithrombin III, but potentially catastrophic exposure of the coronary lesion to activated thrombin may be possible. Some pseudoaneurysms may resolve spontaneously after discontinuation of systemic anticoagulation, despite oral antiplatelet agents. Therefore our practice is to use thrombin injection for femoral pseudoaneurysm resistant to ultrasound guided compression, and treatment is deferred until 48 hours after intervention. We conclude that thrombin injection using ultrasound guidance is poised to replace surgical exploration as the second line treatment for iatrogenic pseudoaneurysm but, particularly for femoral pseudoaneurysm after coronary intervention, further data are necessary before ultrasound guided compression can be abandoned.

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3 Chouhan VD, De la Cadena RA, Nagaswamic C, et al. Simultaneous occurrence of human antibodies directed against fibrinogen, thrombin and factor V following the exposure to bovine thrombin: effects on blood coagulation, protein C activation, and platelet function. Thromb Haemost 1997;77:1223.

Mobile intracardiac calcification: risk of thromboembolism in patients with haemodialysed end stage renal disease

Editor—Tsuchihashi and colleagues describe a number of interesting cases of mobile cardiac calcification in dialysis patients complicated by systemic thromboembolism.7 However, in their discussion of possible pathophysiological mechanisms they fail to mention the possible roles of a number of calcification regulating proteins called Gla proteins. This is a potentially important omission as it may affect management decisions regarding anticoagulation with warfarin.

Work from our laboratory and others has revealed that calcification in the vasculature is not simply a passive degenerative process as was previously thought.8 On the contrary it seems to be a highly complex and regulated process as in bone. Attention has focused on a number of proteins which appear to have regulatory roles during the calcification process and in particular on a group of these proteins known as Gla proteins.9 These Gla proteins are so named because they contain an uncommon amino acid—gamma carboxyglutamic acid (Gla)—formed by a vitamin K dependent posttranslational modification of specific glutamic acid residues. The Gla residues appear to confer calcium binding properties to these proteins. One of the Gla proteins—matrix Gla protein—is thought to act as an inhibitor of calcification since it has been found in intimate association with areas of calcification, and mice lacking this gene have rampant vascular calcification.10

Since metabolic defects in chronic renal failure do not fully explain the presence of extraskeletal calcification, a role for these calcification regulatory proteins is clearly possible. In addition there is in vitro as well as in vivo data from both humans and rats that inhibition of the vitamin K dependent process of Gla residue formation by warfarin may be deleterious, leading to an increase in calcification.11

We feel there are sufficient data to exercise caution in the use of warfarin for the prevention of thromboembolism in the presence of calcification.12

Mobile intracardiac calcification: risk of thromboembolism in patients with haemodialysed end stage renal disease


Rapid Responses now available on eHeart

The full text Heart web site (http://www. heartjnl.com) now has a Rapid Response facility, which means that letters can be “published” on eHeart within seven days of submission.

To send a Rapid Response, please access eHeart and then access the article to which your letter relates. In the top right hand corner of the screen there is a box that contains an invitation to send a Rapid Response (Letters sent to this article). Click on this and then type in your letter or paste it from a word processor. All Rapid Responses are screened within seven days and, provided that they are not obscene, libellous, or unethical, they are then posted on the web site (Rapid Responses are not edited). We will continue to publish in the paper version of Heart all letters that contribute substantially to the literature.

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effect such as increases in arterial, aortic or mitral annular calcification is worthy of investigation.

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The letter was shown to the authors who reply as follows.

As pointed out by Farzaneh-Far and colleagues, many heterogeneous factors such as non-collagenous proteins (Gla protein and vitronectin in atherosclerosis plaques; osteopontin, vitronectin and osteocalcin in cardiac valve calcification), hypertension and aging, diabetes, excess vitamin D3 use, and calcium and phosphate imbalance through hypo- or hyperparathyroidism has been postulated as a possible cause of rapid calcification of the vascular system in end stage renal disease. Recently, Price and colleagues in rats’ and Coates and colleagues in patients with calcific uremic arteriopathy reported the possibility of warfarin related cardiovascular calcification in relation to non-collagenous proteins, Gla.

We do think that the possible contributions of non-collagenous proteins to the rapid cardiovascular calcifications in end stage renal disease should not be neglected in our case studies; however, warfarin has not been prescribed in our cases before obtaining echocardiographic diagnosis. Therefore, warfarin use will not be the main cause of rapid calcifications, at least in our series of cases. Moreover, in case 2 of our study, a surgical specimen revealed fresh red thrombus attaching to cardiac calcification, and any kind of anticoagulation treatment will be essential clinically for preventing short term thromboembolism. Indeed, low molecular weight heparin might be a better therapeutic option in these circumstances, but it also has a limitation in long term clinical use. At this point, monitoring of calcium-phosphate imbalance and the changes of calcification size, warfarin use for preventing thromboembolism will be the most conventional drug treatment in cardiovascular calcification of end stage renal disease. Further studies should be conducted on the cause of rapid cardiac calcification and the possibility of warfarin having a deteriorating effect on cardiovascular calcification.


Instantaneous pressure–flow velocity relations of systemic venous return in patients with univentricular circulation

EDITOR,—We read with great interest the article by Kaulitz et al where Doppler measurements of various venous flows were performed with simultaneous respiratory and venous pressure recordings. The main findings were: venous flow and pressure are dependent on respiration in total cavopulmonary connection (TCPC); and venous flow and pressures are cardiac dependent in atrio-pulmonary connection (APC). While the authors should be commended for monitoring simultaneous flow and pressure data along with respiratory and cardiac monitoring, there were no new insights. Venous flow in the TCPC, by the nature of dissociation from the pulmonary artery blood flow, has been shown to be augmented largely during inspiration since the further decrease of the negative intrathoracic pressures “defers” infow to TCPC antegrade. While venous flow in APC will show less respiratory effect as it is coupled with the atria, it has also long been known to be related to the cardiac cycle.

Importantly, new information might have been gathered by the authors if more subtle pressure–flow relations in TCPC and APC had been described. Theoretically, the relation between pressure and flow allows: evaluation of pathway resistance or vascular impedance, properties of the Fontan circulation that may be crucial to its efficacy. We also have some methodological concerns: the use of maximal antegrade velocity does not take this into account and therefore would not reflect the net or total flow during inspiration or expiration.

Finally, in the evaluation of the haemodynamics of the venous system, particularly in a Fontan circulation where systemic venous return for an univentricular circulatory system. Haemodynamics. 1998;82:294-9. Further studies should be conducted on the cause of rapid calcification and the possibility of warfarin having a deteriorating effect on cardiovascular calcification.

Letters


Surgical therapy for aortic stenosis in severely symptomatic patients older than 80 years: experience in a single UK centre

EDITOR,—There are limitations to the use of increases in serum creatinine as a marker indicative of early postoperative death,1 not least because derangement in this parameter may have more to do with injudicious diuretic dosage in the presence of the unique coexistence of diastolic left ventricular failure and left ventricular outflow obstruction. The use of diuretics for antifailure treatment may, in this context (as in other conditions characterised by diastolic failure), impair the left ventricular filling to such an extent as to precipitate a low output state,1 one consequence being the development of prerenal uraemia. Therefore, if anything, the onset of deterioration in renal function should initiate a shift from medical treatment to surgical intervention, coupled with an interim reduction in diuretic dosage. Surprisingly, notwithstanding the acknowledgement of the existence of an aortic stenosis related syndrome of
low output failure (characterised by pronounced fatigue and debilitation), there is little or no documentation that one of its manifestations could be the syndrome of “aggravated renal dysfunction during intensive treatment for advanced chronic heart failure”.

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Flying after heart surgery

Editor,—The editorial “Flying after heart surgery”,1 is timely and focuses on an important aspect of rehabilitation. One might, however, question the validity of the statement that “Pilots may see cardiac surgery as their only hope . . .” Furthermore, in attempting to explain “the 1% rule”, the defining point between professional fitness to fly on multi-crew operations and permanent unfitness for duty, the authors’ statements need some clarification.

The 1% rule2 requires that the cardiovascular mortality rate of an airman should not exceed 1% per annum, or approximately one event one million hours. This attribution is approximately that of a 65 year old man in northern Europe and will be encumbered by additional non-fatal co-morbid, but potentially incapacitating, events. It does not rely, as Treasure and Janvrin have stated,3 on the impossible incapacitation rate of one event in 1 000 000 000 hours. This figure is the aviation industry target for the “very remote” possibility of an unpredicted (that is, mechanical) adverse event leading to a fatal accident, and is also the target multi-crew fatal accident rate attributable to incapacitation of one of the pilots.4 Employing the 1% rule and maintaining the assumption that only 10% of the envelope of a flight of average duration (100 minutes) is vulnerable with a 1% chance of an event during the vulnerable period leading to an accident, the probability of a multi-crew accident because of a cardiovascular cause is in the order of 1 in 1 000 000 000 hours, a target the industry is on course to achieve.

The most recent and currently used protocols for recertification following cardiac surgery, which are published in the Joint Aviation Requirements—Flight Crew Licensing Part 3 (medical),5 for Europe, require a post index event (surgery, angioplasty, myocardial infarction) delay of six months before recertification can be considered. This differs from the figures derived from the older publications that are quoted by your contributors. Those requiring the text of the JAR-MED, or advice, may write to the Chief Medical Officer, Medical Division, Civil Aviation Authority, Gatwick, West Sussex RH6 0VR, or to the Joint Aviation Authorities, PO Box 20000, 2130KA, Hoofdorp, Netherlands. An up to date bibliography on the subject (not cited) is included in the Second European Workshop in Aviation Cardiology.6

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The letter was shown to the authors who reply as follows:

Our editorial in Heart does discuss an aspect of rehabilitation after cardiac surgery, albeit a very narrow one. Pilots often see cardiac surgery as their only hope of regaining a licence to fly, and in this context we consider our statements to be valid.

We are not sure that Professor Joy’s clarification of the 1% rule adds much to what we wrote on a “need to know” basis for cardiac surgeons. Both he and we state the same thing. To the travelling public, a reassuringly small chance (1 in 1 000 000 000 hours of flying) of a pilot’s incapacity leading to a fatal aircraft accident is met by that pilot (and the co-pilot) having less than a 1% risk of a myocardial event in a year.

We are not in a position to comment on post surgery criteria that must be achieved to meet that risk. These are the criteria published in the current European Joint Aviation Requirements,1 which states that “. . .subjects may be considered for recertification [after cardiac surgery] upon the impossible incapacitation rate of one event in 1 000 000 000 hours. This figure is the aviation industry target for the “very remote” possibility of an unpredicted (that is, mechanical) adverse event leading to a fatal accident, and is also the target multi-crew fatal accident rate attributable to incapacitation of one of the pilots. Employing the 1% rule and maintaining the assumption that only 10% of the envelope of a flight of average duration (100 minutes) is vulnerable with a 1% chance of an event during the vulnerable period leading to an accident, the probability of a multi-crew accident because of a cardiovascular cause is in the order of 1 in 1 000 000 000 hours, a target the industry is on course to achieve.

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The letter was shown to the authors, who replies as follows:

The use of verapamil to prevent radial artery spasm has been one of the most important advances in the development of the transradial technique. Earlier studies, including those reported by Dr Hildick-Smith et al, used only nitrates, or sublingual nifedipine, or both to prevent such spasm, and verapamil is a substantially more effective agent.7 The intra-arterial administration is immediately less painful and would be given before sheath advancement. The radial artery is extremely sensitive to circulating catecholamines.8,9 Thus, spasm may be provoked or accentuated by anxiety and pain in addition to mechanical manipulation. In this regard, the importance of adequate sedation and analgesia cannot be overemphasised. Other tips regarding management of radial artery spasm can be found on Dr Kiemeneij’s website (www.radialforce.org).

The above preventative measures have virtually eliminated the problems noted by Dr Hildick-Smith et al. The incidence of radial artery access failure should be less than 5%,10,11


Pre-excitation or post-excitation

Editor,—We read with great interest the case study by Lau et al entitled “A new ECG sign of an accessory pathway in sinus rhythm: pseudo partial right bundle branch block”. However, ventricular pre-excitation can change any part of QRS, the sole terminal portion change is very rare. In the demonstrated case, the authors stated that the pseudo partial right bundle branch block was the only manifestation of the left sided accessory pathway. However, in the V3 leads, the PR seems to be shortened and the initial portion of QRS complexes can be interpreted as delta waves (fig 1).

On the management of scorpion stings

Editor,—We read with great interest Karndad’s paper,1 and also the responses in the correspondence columns concerning the same article. We have the following points to make based on our 12 years’ experience of scorpion envenomation in experimental animals. According to Karnad’s study,2 scorpion envenomed patients exhibited haemodynamic changes in terms of right or left ventricular failure. However, our results with experimental animals have shown two stages of envenomation—namely, a stage of immediate respiratory failure and a delayed stage of circulatory failure.3 Respiratory failure occurred within two to three minutes in all 10 of the animals we studied. Nearly 40% of them died within five minutes; the remaining 60% recovered from the initial respiratory arrest and survived for one to three hours. In this 60%, however, respiratory never returned to normal, and it was associated with ischaemia-like ECG patterns. At the same time, the mean arterial pressure gradually decreased until it dropped abruptly along with respiratory arrest. Eventually, ventricular fibrillation occurred resulting in the animal’s death. The initial stage appears to be mediated by the neuronal components, as reported elsewhere.4 The circulatory failure may be due to increased kinins decreasing the blood pressure, or to irreversible shock syndrome associated with multiorgan failure, or myocardial ischaemia leading to ventricular failure. At this stage, we have observed increased secretions (lacrimation, salivation, and tracheal secretion), passing of urine and stool, etc. Our results indicate that respiratory failure is more crucial in determining the mortality and time of death than circulatory failure. We are not able to comprehend the exact mechanisms by which captopril reverted the circulatory derangements and the improvement of scorpion stung patients.5 Rather, we anticipated a fall in blood pressure with captopril, as it increases endogenous kinin concentrations. We have showed that captopril mimics the action of venom.6 However, Karnad and Bawaskar7 missed our reports on *Buthus tamulus* envenomation.8 Further, it has also been shown that kalikrein-kinin inhibitor (aprotinin) countered the scorpion toxicity.9 In addition, we have shown that scorpion venom increased the afferent vagal activity that can be blocked by aprotinin.10 This evidence indicates that aprotinin blocks the underlying pathology of scorpion envenomation, and is therefore better than other drugs for treating envenomation. Prasozin, an α1 adrenergic receptor blocker, can only block the increased adrenergic activity seen after envenomation at the postsynaptic sites, but it cannot reverse the underlying pathology generated by kinins or other mediators. Contrarily, there are reports of the successful use of insulin11 in patients stung by scorpions, and these reports do not find a place in the discussions of Karnad12 or Bawaskar.13 Therefore, we feel that insulin still has a place as a therapeutic agent in the treatment of scorpion toxicity unless disproved otherwise.

Regarding pulmonary oedema associated with scorpion envenomation, we have recently demonstrated pulmonary oedema after *Buthus tamulus* envenomation (detected by physical and histological evidence).14 Further, pulmonary oedema was due to the involvement of kinins as pretreatment and aprotinin, which blocked the venom-induced pulmonary oedema and other features of scorpion toxicity.15 The decreased ventilation seen at this stage of delayed circulatory failure further favours the formation of pulmonary oedema.

In conclusion, captopril should be avoided in the treatment of scorpion toxicity until we understand the precise mechanisms behind its action. Aprotinin is a better choice as it blocks or counters the pathophysiological processes of scorpion envenomation and is also easily available in developing countries like India, where antivenom has yet to find a place in the market. The proven efficacy of insulin has to be considered with greater openness for the benefit of scorpion stung patients.

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6 Bagchi S, Deshpande SB. Indian red scorpion (*Buthus tamulus*) venom-induced augmentation of cardiac reflexes is mediated through the involvement of peripheral 5-HT, and central 5-HT2 receptor subtypes. *Toxicon* 1999;37: 1697–709.

This letter was shown to the author and Dr Bawaskar responds as follows:

Our experience and rational approach to the management of life threatening, acute medical emergencies caused by scorpion envenomation is entirely different, and we do not agree with the use of aprotinin advocated by Deshpande and Alex. Aprotinin is not available in India; it is currently only licensed.
for cardiac operations that have a large risk of perioperative bleeding. In human scorpionism, which is entirely different from experimental, the clinical manifestations are related to many factors such as the weight of the victim, the size of the scorpion, the season, and the time lapsed between sting and administration of prazosin. By the time they are hospitalised, all patients exhibit cardiac arrhythmia once prazosin had taken effect. Respiratory failure is a secondary phenomenon.

Scorpion venom stimulates neuronal sodium channels, resulting in autonomic storm. Both branches of the autonomic system are stimulated, resulting in vomiting, sweating, salivation, fasciculations, priapism in men, hypotension, hypertension, bradycardia or tachycardia, ventricular premature contractions, cool extremities, pulmonary oedema, and shock (fig 1).

It has been proved beyond doubt that pulmonary oedema, as a result of scorpion envenomation, is due to myocardial dysfunction. Bradykinin induced secretory pulmonary oedema is secondary, and occurs as a result of the stimulation of kalikrein due to tissue damage caused by anoxia and the accumulation of oxygen free radicals, if cardiogenic manifestations are not managed earlier with prazosin.

Receptor stimulation plays an important role in the pathogenesis of scorpion stings resulting in an inotropic (hypertension) phase, which, if not treated, progresses to a hypokinetic (pulmonary oedema, hypertension, tachycardia, and shock) phase. The hypokinetic phase is due to the liberation of oxygen free radicals, fatty acids, and insulin deficiency. Prazosin enhances insulin secretion by blocking α receptors over β cells of the pancreas. Hyperkalaeamia and hyperglycaemia exist in the victim due to autonomic storm. Prazosin increased endogenous insulin secretion thus acts like a glucagon–insulin potassium drip and protects and prevents myocardium injury caused by liberated fatty acids and oxygen free radicals, and prevents lethal cardiac arrhythmia and sudden death (fig 2).

Atropine, which is similar to aprotinin, enhances cardiovascular morbidity and mortality by blocking acetyl choline action (vagolytic).

Recently, Abroug et al reported that scorpion antivenom is no better than placebo. Similarly, in our series, scorpion antivenom (available since 1997) did not prevent cardiovascular manifestations as a result of *Mesobuthus tamulus* sting. Primary care doctors need full understanding of pathophysiology and a rational approach to this type of medical emergency to avoid high morbidity and mortality.

Prazosin, a pharmacological antidote to venom, which reverses both inotropic and hypokinetic phases induced by severe scorpion stings, is simple, scientific, easily available, and does not cause anaphylaxis. Since its advent, mortality due to scorpion stings has been reduced to less than 1%. It should be the first line of treatment for severe scorpion stings.

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10 Bawaskar HS, Bawaskar PH. Envenoming by scorpions and snakes (elapidae), their neurotoxins and therapeutics. *Top Doct [in press].

Dr Carey Coombs and his non-existent cardiac infarct

EDITOR.—Carey Franklin Coombs, 1879–1932, was a physician at the Bristol General Hospital. He made important studies of rheumatic fever describing the diastolic murmur of acute rheumatic mitral valvulitis, which bears his name, and taking a great interest in the prevention and management of heart disease in children. His 1924 monograph *Rheumatic heart disease* became a standard work on the subject. He also did pioneering work in coronary heart disease, and around 1910 he made a clinical
diagnosis of coronary thrombosis at a time when the condition was almost unheard of. His patient survived, so without necropsy proof he did not achieve priority of recognition, which went to James Herrick of Chicago in 1912. His interest in the disease continued, and by 1932 he had studied and published 144 cases of coronary thrombosis.

His own illness
In 1932, aged 53, he stopped with chest pain while walking up a steep hill. A short time later, he had an unheralded syncopal attack and was admitted to hospital. On recovery he had no pain. The ECG showed bundle branch block and a diagnosis of coronary thrombosis was made. As was then the rule, he was kept in bed for six weeks. He was then allowed up, but suddenly fell down dead.

Carey Coombs's medical registrar at that time was C Bruce Perry (1903–96), who later became the professor of medicine in Bristol. It was he who told me about Coombs's illness and its aftermath. On the day before the funeral, Mrs Coombs asked Perry to remove her husband's heart saying that it had been his wish to have it placed in the pathology museum. By then the body was in a coffin in Coombs's consulting room, but Perry unscrewed the lid and took out the heart with the help of a postmortem technician. Perry, a young registrar aged 29, was then presented with a dilemma that he later wrote about: “Externally the heart looked normal. I did not know what to do, or to say to the people who had looked after him. Geoffrey Hadfield [then pathologist at Barts having been previously in Bristol] was coming to the funeral so I phoned him and he agreed to ‘demonstrate’ the heart to the senior physicians afterwards. This he did showing them an infarct that was not there but they were satisfied. When they had gone he gave me the heart and said ‘now find out what was wrong’. We took sections of all parts histologically and finally found a small lesion in the region of the AV bundle. I am afraid there was nothing to put in the museum. Looking back on it I think he had a Stokes-Adams attack when he fell unconscious and a massive pulmonary embolism when he died. But of course we did not examine the lungs so we shall never know. One should not agree to a partial incomplete examination if one wants to get as near as possible to the truth” (personal communication).

Another domiciliary necropsy done by Bruce Perry
One of the cases in the 1932 paper was a man whom Carey Coombs had seen in the patient's home in 1928, in consultation with the general practitioner. There was then no portable ECG to support the clinical diagnosis. The patient died and Perry recounted that he was sent to get the heart: “I took knives etc from the postmortem room and lots of old newspapers. The body was lying on a bed and as I lifted it onto the floor covered in newspapers a wig fell off. The general practitioner was present and said, ‘Oh dear, I have known him all these years and did not know he had a wig.’” The heart when opened showed a classic infarct which Coombs had photographed, but apparently never published.

An excellent and full account of Carey Coombs's life and work has been written by Clive Weston,1 and his influence lives on in Bristol with a research scholarship named after him.

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IMAGES IN CARDIOLOGY

Onset and termination of atrial fibrillation

Ectopic atrial activity may be a mechanism of onset of some forms of atrial fibrillation (AF). This ECG from a 77 year old man shows triggering and termination of AF. AF is present at the start but rapidly terminates. During sinus rhythm atrial extrasystoles (arrows) reinitiate short bursts of AF. A third atrial extrasystole (*) is not conducted. The P wave morphology and axis of the triggering ectopic beats suggested focal activity close to the right superior pulmonary vein. During a treadmill exercise test AF was initiated by an atrial extrasystole and sustained for 16 minutes. Subsequent Holter monitoring revealed frequent atrial ectopy (239 per hour) and 11 episodes of AF lasting from a few seconds to 4.8 minutes. No other aetiology for AF was found. Recognition of this focal mode of onset of AF in the otherwise normal heart is important since radiofrequency ablation is potentially curative.

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PETER A BRADY
JOSEPH L BLACKSHEAR