Sclero-calcific mitral valve changes in patients with chronic renal failure on haemodialysis

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Cardiovascular disease is common [1] and the principal cause of death in patients with end-stage renal disease on long-term dialysis therapy. Cardiac involvement in such patients may manifest as pericarditis, accelerated atherosclerosis with resulting angina or myocardial infarction, hypertensive heart disease or dilated (congestive) cardiomyopathy. However, many physicians and even cardiologists are unaware that important mitral valve abnormalities can occur in patients with chronic renal failure (CRF), since the reports describing such lesions are recent and few in number [2-5]. Although rare, mitral valve pathology of this nature has been well documented at autopsy [3-5] and is readily detected by echocardiography [5-8].

Mitral calcification

Calcification at the base of the posterior mitral leaflet, sometimes referred to as the posterior mitral annulus region, is frequently visualised on echocardiography in CRF patients on long-term haemodialysis. This calcification appears very similar in location to the senile degenerative type of 'mitral annulus calcification' (MAC) often observed in the elderly population, especially women [9,10]. On the M-mode tracing, the calcification is manifest as a dense band between mitral valve and left ventricular posterior wall (Fig. 1). On the two-dimensional echocardiogram, it is represented by a dense round or oval echo at the base of the posterior mitral leaflet in the long-axis view; in the short-axis and apical four-chamber view, the calcification is seen as a dense bar or crescent closely adjacent to (and sometimes partly embedded in) the left ventricular postero-basal wall (Figs 1 and 2).

Although the general anatomical location of senile MAC is very similar to that of MAC in patients with CRF and the echocardiographic appearances are also similar, our autopsy observations [11] indicate that several differences exist between the two groups of patients. These differences, set forth in Table 1, await confirmation from other workers.

| Table 1. Differences between ‘mitral annulus calcification’ of CRF and of the senile degenerative type. |
|---------------------------------------------------------------|
| **Age** | **Sex** | **Chronic renal failure** | **Senile degenerative** |
| --------- |--------|---------------------------|------------------------|
| Over 25 years | No conspicuous sex predominance | Over 55 years | Conspicuous female predominance |
| Posterior MAC | Aggregation of rounded polyoid excrescences (Fig. 3) | Solid compact bar in severe cases | Small calcific nodules or ridge in mild cases |
| Anterior mitral leaflet | Sometimes heavily calcified at its base | Never heavily calcified. Mild to moderate calcification occasionally seen in extreme old age |

- Aortic valve
- Calcification not common
- May occur in chordae tendineae, papillary muscle or trabeculae

- Hyperparathyroidism
- Always present
- Absent

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The prevalence of MAC in a large unselected population of CRF patients on dialysis is uncertain. The prevalence of MAC in CRF patients referred for echocar-
Fig. 1. (Top) M-mode echocardiogram in a chronic renal failure patient showing 'mitral annulus' calcification of mild to moderate extent as a dense band between the mitral valve leaflets (MV) and the left ventricular posterior wall (LVPW). (Bottom) 2-D echocardiogram in the same patient showing calcification at the base of the posterior mitral leaflet in the parasternal long-axis view (left). The calcification is also seen in the apical four-chamber view (right). RV—right ventricle; LA—left atrium; ECG—electrocardiogram; VS—ventricular septum; AO and AR—aortic root.

Fig. 2. 2-D echocardiogram in the parasternal long-axis view (left) and short-axis view (right) of a patient with chronic renal failure. Calcific thickening (CAL) is seen at the base of the anterior as well as posterior mitral leaflets. RV—right ventricle; LV—left ventricle; AR—aortic root; VS—ventricular septum.
diography (for suspected cardiac involvement) was 26 per cent in the series of D'Cruz et al. [7] and 9.5 per cent in that of Forman et al. [12]. Terman et al. described intramyocardial calcification in the hearts of six autopsied CRF patients [13], but did not mention finding mitral calcification in any.

A rare but remarkable form of mitral calcification has been well documented recently [2-5] as a complication of CRF in patients on long-term dialysis. Large calcific deposits are present in the basal part of the anterior as well as posterior mitral leaflet; the free edges of the mitral leaflets and their chordae tendineae are spared. Radiography of the excised heart may demonstrate a complete or almost complete calcific ring encircling the mitral orifice (Fig. 3) [4]. Mitral orifice stenosis can develop and progress over a period of months or years [2]. An apical diastolic murmur typical of rheumatic mitral stenosis may be heard. The M-mode and two-dimensional echocardiographic appearances are unusual and highly characteristic (Fig. 4): both mitral leaflets appear very dense, thick and immobile near their attachment to the mitral ring; however, the normal pattern of mitral leaflet motion may be recorded at their free edges. We have encountered five CRF patients on dialysis for periods from two to 14 years who had this type of extensive mitral valve calcification shown on echocardiography. In two, the lesions were confirmed at autopsy; the distribution of calcification, gross morphology and histology of the mitral valve were very different from those encountered in calcified rheumatic valves. DePace et al. demonstrated mitral stenosis in their patient by invasive haemodynamic studies [2]. We have observed, with serial echocardiograms, the gradual progression of similar lesions in a 52-year-old woman (I.B.) on dialysis over a period of 11 years. Mitral calcification was absent on M-mode echocardiography in the first year of dialysis; in the eleventh year of dialysis, M-mode and two-dimensional echocardiography revealed heavy calcification of the base of both mitral leaflets, and Doppler echocardiography demonstrated mild mitral stenosis (estimated mitral orifice area 1.8 cm²). Serial electrocardiograms in the twelfth year of dialysis revealed the appearance of first-degree A-V block, then 2:1 A-V block and later high-grade A-V block, requiring implantation of a permanent pacemaker (the patient was not on digitalis or other cardiac drugs). It is possible that the calcification in the region of the base of the anterior mitral leaflet encroached upon the A-V conduction pathway in the region of the membranous interventricular septum. To our knowledge, the association of A-V block with mitral calcification of CRF has not been previously reported, although the association of MAC of the senile degenerative type with A-V block is well known [14, 15].

Mitral calcification in CRF patients on dialysis can take forms other than massive annular-type calcification as described above. Thus, an isolated calcific nodule was noted in one case in the middle of the anterior mitral leaflet [5]. Calcification in a papillary muscle, chorda tendineae or even in left ventricular trabeculae has been noted by us [11].

The pathogenesis of mitral calcification in CRF patients on long-term dialysis is very likely to be related to altered calcium metabolism secondary to hyperparathyroidism [16]. Elevated blood parathyroid hormone levels are the rule in such patients; those with mitral calcification have higher levels than those without such calcification [17]. Systemic hypertension may also predispose to mitral calcification in this setting [10]. We have noted that CRF patients with the most extensive mitral calcification sometimes have extensive soft-tissue calcification around elbow or shoulder joints and in the walls of large arteries that can be seen on X-ray [17].

### Fibrous changes in mitral chordae

We could find no published information on this topic prior to our report of four autopsy cases [5]. The mitral chordae showed irregular thickening and shortening affecting some chordae tendineae and sparing others (Fig. 5). Histologically, the affected chordae showed concentric rings of loose connective tissue around a central dense axial core [5]. In three cases, the mitral valve leaflets were normal or showed only slight thickening; the fourth had considerable leaflet thickening. Mitral chordal thickening can be visualised on M-mode and two-dimensional echocardiography [5] (Fig. 6). Such mitral pathology could possibly account for apical systolic murmurs, sometimes heard in CRF patients. One of our patients had severe mitral regurgitation, demonstrated by cardiac catheteri-
sation (Fig. 6) and cineangiography, for which there was no other obvious cause at autopsy.

The aetiology of these fibrotic mitral changes, principally involving the chordae tendineae, is uncertain. The gross anatomical distribution of the fibrotic thickening and the histological appearances are very different from rheumatic mitral scarring. Certain other causes of mitral apparatus thickening, including mucoid degeneration, carcinoid disease, Hurler's syndrome, Marfan's syndrome, and methysergide therapy could not be incriminated in our CRF patients. Other suggested factors include: (a) prolonged exposure to toxic metabolites of uraemia; (b) cumulative irritant or noxious effects of chemical contaminants (present in trace amounts in the water used during haemodialysis); and (c) subclinical viral infection, possibly chronic or recurrent, in CRF patients who have lowered host defences.

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Fig. 5. Close-up photograph at autopsy of the mitral chordae tendineae of two different patients with CRF. Note the grossly abnormal chordal thickening, which, however, spares some chordae; the latter retain their normal thin delicate appearance (left panel). The free edges of the mitral leaflet are seen at the top of the photographs.

Fig. 6. 2-D echocardiogram in the parasternal long-axis view (left) and short-axis view (right) of a patient with chronic renal failure and mitral regurgitation. Arrows indicate the thickened mitral chordae tendineae. RV—right ventricle; LV—left ventricle; LA—left atrium; AR—aortic root.