Pathophysiology of hypertrophic cardiomyopathy

Sir—A J Marian (Jan 1, p 58)[1] postulates that cardiac contractility is decreased in hypertrophic cardiomyopathy (HCM) and that the preserved or increased ejection fraction observed in patients with HCM is a result of the concentric nature of the hypertrophy. Marian predicts that study of young patients with familial HCM will reveal decreased myocyte contractility and postulates that insulin-like growth factor-1 (IGF-1) is upregulated and a major contributor to the pathological manifestations of HCM.

To test these predictions we looked at echo-cardiographic measurements on our data bases of normal children and children with concentric left ventricular hypertrophy of different aetiologies. In the table we compare normal infants (InfCon; mean [SD] age 0·30 [0·30] years), with infants of diabetic mothers with secondary hypertrophic cardiomyopathy (InfDM; age 0·02 [0·04] years) and with infant presentation of primary HCM (InfHCM; age 0·34 [0·30] years). The infants with primary HCM do not show any reduction in contractility and, indeed, their ejection fraction is significantly higher than that of normal infants. This result is not simply secondary to concentric hypertrophy since the infants of diabetic mothers, which display non-dilated hearts with hypertrophy of the same magnitude, show ejection fractions that are lower than those of normal infants and of infants with true primary HCM. Secondly, we compare prepubertal children with familial non-obstructive HCM (FamHCM; mean age 3·7 [3·6] years) with normal children (ChildCon; age 4·3 [3·4] years) and with children with compensatory concentric cardiac hypertrophy occurring in response to valvar aortic stenosis (AoSten; age 3·3 [0·9] years. This comparison shows that young patients with mild HCM, with a wall thickness still well within normal limits for adults, already have increased systolic contractility compared with normal children and the same contractility as hearts working against a fixed obstruction (table).

There seems to be no evidence to support the contention that myocardial contractility is decreased in HCM. Furthermore, concentric hypertrophy caused by excess of insulin and IGF-1 is associated with reduced rather than increased ejection fraction. An alternative hypothesis to that of Marian's for explaining the pathophysiology in HCM is that the abnormal contractile proteins associated with HCM trigger a reflex increase in sympathetic nervous activity to the heart, possibly because of alterations in characteristics of diastolic filling. Increased cardiac sympathetic nervous activity is probably the final common pathway in the induction of most forms of adaptive cardiac hypertrophy, including pressure-overload of the left ventricle.[2] In keeping with our hypothesis, it has been shown that increased activity of cardiac sympathetic nerves occurs in patients with HCM.[3] The attraction of our hypothesis is that it offers a clinical approach to modify disease progression with pharmacological intervention: administration of high-dose β-adrenoceptor antagonist therapy. Such treatment does seem to reduce disease progression,[4] and is associated with significantly better survival in patients with childhood presentation of hypertrophic cardiomyopathy.[5] In view of the striking survival advantage seen in children, high-dose β-blockade deserves wider evaluation in adult HCM too.

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Group	Mean septum thickness (cm, SD)	Mean LV wall thickness (cm, SD)	Mean ejection fraction (SD)
InfCon (n=38)	0·47 (0·07)	0·39 (0·07)	0·76 (0·06)
InfHCM (n=12)	0·96 (0·26)	0·65 (0·17)	0·88 (0·06)*
InfDM (n=9)	0·82 (0·31)	0·58 (0·16)	0·65 (0·12)*†
ChildCon (n=174)	0·57 (0·12)	0·53 (0·13)	0·75 (0·05)
FamHCM (n=16)	0·91 (0·18)	0·61 (0·16)	0·83 (0·04)*
AoSten (n=10)	0·82 (0·20)	0·70 (0·17)	0·84 (0·04)*

*Different from controls (p=0·008–0·0001, Mann-Whitney U-test).
†Different from InfHCM (p=0·0003).

Comparisons of myocardial contractility in different forms of cardiac hypertrophy

Role of microvascular decompression in trigeminal neuralgia

Sir—The hypothesis that a mild or severe vascular contact at the trigeminal root entry zone is responsible for idiopathic trigeminal neuralgia is not credible.[1,2] All studies of microvascular decompression do not have adequate controls, and this omission generally biases in favour of the treatment. Giovanni Broggi and colleagues (Nov 27, p 1878)[3] propose a role for microvascular decompression in multiple-sclerosis (MS)-associated trigeminal neuralgia on the basis of what seems to be poor science.

Although not clearly stated, all 15 of their patients had microvascular compression: this is good luck on their part. Indeed, there are patients with idiopathic trigeminal neuralgia who do not have microvascular compression.[1,2] A magnetic resonance imaging (MRI) study of this condition identified microvascular compression in only 53% of cases.[4] Broggi and colleagues report an excellent outcome in seven of 15 patients (including a reoperation) with a mean follow-up of little more than 2 years. This improvement in 47% of patients over 2 years compares unfavourably with 70% over 10 years.[3] After questioning the effectiveness of their surgery, these workers suggest a dual cause for MS-associated trigeminal neuralgia, disregarding simple statistical rules. Instead of multiplying the number of possible causes, they should have been wise to notions such as the null hypothesis assumption regression to the mean of the disease and possible placebo effects of surgery. Randomised-controlled studies remain the gold standard in evidence-based medicine: the highly popular mammary artery ligation and intracranial-extracranial bypass for angina pectoris and stroke prevention collapsed on placebo effect or when compared with other therapies.

If one espouses the microvascular compression hypothesis, the three

patients with trigeminal neuralgia and no plaque on MRI (see their table) had idiopathic trigeminal neuralgia and not MS-associated trigeminal neuralgia. The remainder had both plaques and microvascular compression. Which one was responsible? Occam's razor suggests the former, especially if we take into account those studies of MS-associated trigeminal neuralgia in which MRI disclosed a plaque but no microvascular compression.[5] Also, trigeminal neuralgia is frequent in MS because MS is a progressive disease with a tendency for plaques to spread to all brain tissues over time. Moreover, microvascular compression can be both mild and severe. Does mild compression have equal standing to severe compression in their purported mechanism?

Microvascular decompression is not such a safe procedure as its supporters claim: it has 0·5% mortality and up to 10% morbidity. Let us not add another myth to the growing fiction about microvascular compression.

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Authors' reply

Sir—Vincenzo Bonicalzi and Sergio Canavero have some misconceptions about our report. First, the hypothesis that a vascular compression could be involved in the pathogenesis of idiopathic trigeminal neuralgia is debatable, but is generally accepted and it can be neither definitely proved nor definitively denied. Second, obviously randomised-controlled studies are the gold-standard in evidence based medicine. Nevertheless, clinical retrospective studies are the first step towards clear statistical evidence, and regression to the mean is one of the biases of this kind of investigation. The lack of controlled studies about any surgical treatment of trigeminal neuralgia shows the difficulties in randomising patients with otherwise untractable pain who are imploring us for effective surgery. Third, we and others have never noted a placebo effect of surgery in trigeminal neuralgia. Additionally, percutaneous procedures unfortunately do not result in pain relief. Fourth, with respect to the percentage of patients with vascular compression, in this series we identified severe and indisputable compression in nine of 15 cases. The rest had contact without root distortion. Furthermore, the rate of MRI-detected vascular compression might be different from the neurovascular relations found at microsurgical exploration. Last, MS-associated trigeminal neuralgia is well known to be much more difficult to treat than idiopathic disease. The comparison between results of treatment of idiopathic trigeminal neuralgia and our results in MS patients is misleading.

As to pathogenesis, we and others[1] recorded vascular compression in MS-associated trigeminal neuralgia. Occam's razor would suggest MS as the unique cause if there were not clear evidence that vascular compression is associated with focal loss of myelin.[2] We think there is only one trigeminal neuralgia and not idiopathic and MS-associated forms. Pain paroxysms are the result of the interaction between pathological inputs from the zone of vascular compression[3] and pathological hyperactivity of trigeminal nucleus. In some cases central damage with spontaneous ectopic excitation foci may be the only cause of trigeminal neuralgia (MS patients with plaques along trigeminal pathways without any vascular compression at trigeminal REZ exploration). In other cases, peripheral damage due to severe vascular compression might be sufficient to kindle trigeminal pain (most of the so-called idiopathic form). Hence, some idiopathic and classic MS-associated trigeminal neuralgias would seem to be the two extremes of the same disease. In between, there might be idiopathic disease without severe vascular compression (supposed predominant central alteration), and MS-associated pain with moderate or severe vascular compression.

In reply to Bonicalzi and Canavero's last point, in the past 20 years we have done more than 2000 percutaneous procedures[4] and more than 400 microvascular decompressions[5] for trigeminal neuralgia with no deaths. As to morbidity, no patient had their quality of life severely compromised by microvascular decompression, whereas about 2% of patients who underwent percutaneous procedures had their lives blighted by neuropathic pain. Let us not allow prejudice to deny an ad hoc MRI protocol that can offer a therapeutic option to patients with MS-associated trigeminal neuralgia.

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Therapeutic efficiency of tirofiban in acute coronary syndromes

Sir—Christopher Heeschen and colleagues (Nov 20, p 1757)[1] describe the role of cardiac tropinin (cTn) I and T in the diagnosis and risk stratification of patients with acute coronary syndromes. cTnI values of more than 1·0 μg/L were associated with an increased risk of cardiac events and identified those patients likely to benefit from tirofiban. However, the method to determine cTnI and the diagnostic threshold for cTnI of 1·0 μg/L used may have caused flaws in the study. Inter-method differences in serum cTnI determination exist and there is no clear standardisation of cTnI immunoassays.[2,3] Of particular