by foam cells was not significantly different between r-hirudin-treated and heparin-treated animals that were killed 2 hours after angioplasty (0% versus 3±6%, p=0.18). However, among the arteries of rabbits killed 28 days after angioplasty, those treated with r-hirudin had a significantly lower percentage of plaque occupied by foam cells compared with heparin controls, even when the analysis included only those arteries that were patent at 28 days (r-hirudin, 2±4%, n=12 versus heparin, 17±14%, n=10; p=0.002). As mentioned in our article, we agree that the lower percentage of foam cells in r-hirudin animals might be related to its antithrombin effect, particularly in view of observations that thrombin promotes monocyte adhesion to the vessel wall, but we have no direct evidence for this. However, we have found a clear positive correlation between the percentage of foam cells in the plaques of these vessels and the percent luminal cross-sectional area narrowing by plaque (correlation, R=0.74). Thus, the high percentage of foam cells seen in the artery depicted in Figure 6 may be related to its severe narrowing, but whether this relation is a manifestation of the incorporation and organization of mural thrombi is not certain. The relation between thrombin-dependent mechanisms, foam cell infiltration, and intimal hyperplasia is being studied by our group.

Total occlusions do occur in this rabbit model after balloon angioplasty. In our subsequent experience using the same dose of heparin (150 units/kg) at the time of angioplasty (without aspirin), these occlusions have occurred in three of 39 arteries (10.3%), which is not too dissimilar from that reported from the Thorax-center in humans (5.3%). Because total occlusions also occur after initially successful balloon angioplasty in humans, it seemed reasonable to include these arteries in our original report. However, the major findings of our study also apply to arteries that remained patent at late follow-up.

No animal model exactly reproduces the complexity of balloon angioplasty of atherosclerotic coronary arteries in humans. Human trials in restenosis, however, are extraordinarily expensive, and the number of potential therapies is enormous. Therefore, trials of potential therapeutic agents in animals are appropriate and important. Furthermore, the fundamental pathobiology of vascular injury and healing is poorly understood. The model used in these experiments has certain features that may make it particularly applicable to human angioplasty. This model studies the effects of balloon angioplasty on preexisting atherosclerotic plaque that have only 2-4% foam cells at baseline and are similar histologically to the noncalcified atherosclerosis seen in young adults. It is known that the response to vascular injury is different in such arteries compared with normal arteries. Indeed, Mustard et al have shown that thrombosis is more prominent after second arterial injury.

In conclusion, we believe that our data support the hypothesis that r-hirudin reduces restenosis after balloon angioplasty in atherosclerotic femoral arteries in hypercholesterolemic rabbits. We believe that animal models are important in the investigation of restenosis after balloon angioplasty, and that the various models currently in use provide unique perspectives in understanding the pathobiology of healing after vascular injury.

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Length-Sensing Function of Troponin C and Starling’s Law of the Heart
In a recent article in the Research Advances Series, Parmacek and Leiden review the current state of definition of the structure, function, and regulation of the TnC gene expression and expose the importance of the potential use of molecular biological technology in this field. In doing so, however, the work of my group was inadequately represented. In our original report in 1988, Babu et al published results observed after the exchange of 70% of cardiac TnC in skinned cardiac muscle trabeculae with skeletal TnC. A marked decrease in the length dependence of contractile force at submaximal Ca2+ concentrations was observed in these cardiac muscle preparations. We thus suggested that cardiac TnC played an important role in the length-sensing mechanism in cardiac muscle in addition to its role as the on-off Ca2+ switch for contraction.

Parmacek and Leiden raised three criticisms of this work: First, they questioned whether the addition of skeletal TnC to the extracted cardiac muscle trabeculae was “stoichiometric.” Second, they claimed that the results were obtained from a “small number of preparations.” Third, they noted that, in contrast to the results reported in our original publication, stoichiometric replacement of skeletal TnC with cardiac TnC, in fast switch fibers, had been demonstrated by a second group to have no effect on the length dependence of Ca2+-activated tension. This conclusion, based on a report published in abstract form at the time of submission of the review, was therefore used to question the validity of our published results. However, omitted were three separate communications indicating that exchange of skeletal TnC for cardiac TnC in fast fibers did enhance their length dependence of contractility. Full-length studies addressing these issues have now been published by both laboratories.

In response to the first criticism, stoichiometric exchange of distinct TnC isoforms has been demonstrated by my laboratory. Silver-stained gels analyzed densitometrically were used to quantitate the exchange stoichiometry. When cardiac TnC recoveries were normalized to the density of LCI band, ratios of 0.31 and 0.09 were observed in native (unextracted) and extracted trabeculae, respectively. A ratio of 0.09 was also observed in extracted trabeculae reloaded with skeletal TnC; in extracted trabeculae reloaded with cardiac TnC, the ratio observed was 0.33 (see Table 1 in Reference 2). Because the skeletal TnC band overlapped with the cardiac LC2 band, the amount of skeletal TnC reloaded in extracted trabeculae could also be estimated by subtraction. A difference of 0.15 was observed, which when adjusted for the established lighter staining of skeletal TnC compared with that of cardiac TnC (1.00:1.4), by accounting for a density ratio of 0.21. Thus, the density ratio of the total TnC content in the extracted trabeculae reloaded with skeletal TnC was 1.00:1.4.
TnC was 0.21 plus 0.09 (reloaded skeletal TnC plus residual cardiac TnC), or 0.30 — a figure not significantly different from that in the native fiber or that in extracted trabeculae reloaded with cardiac TnC. These published figures therefore indicate stoichiometric exchange of the respective TnC moieties. Similar results were obtained in nine trabeculae—a number that invalidates the second claim that stoichiometric exchange was observed in only a “small number of preparations.”

The lack of citation of available evidence by Parmacek and Leiden, critical in all three arguments presented, has led to some inaccuracy in the conclusions made and also to an underestimate of the full potential of the combination of molecular biological technology and skinned muscle fiber approach to the identification of the molecular mechanisms of contraction.

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Reply
We appreciate the comment by Dr. Gulati concerning our recent review of the structure, function, and regulation of troponin C.1 The purpose of any review is to present all of the relevant data in a fair and balanced fashion. In addition, it is important to identify areas of controversy and to suggest experiments that might be used to resolve such controversies. As pointed out by Dr. Gulati, the role of cardiac troponin C in determining the Starling properties of cardiac muscle is clearly this type of controversial area. Accordingly, in our review, we carefully referenced data from Dr. Gulati’s group2 that suggested an important role for cTnC in determining Starling properties as well as work from Dr. Moss’s group,3 which suggested that cTnC does not play an important role in determining length–tension relations in cardiac muscle. As described by Dr. Gulati, subsequent articles from both groups have continued to emphasize the controversial nature of this problem.4,5 We also pointed out in the review that transgenic animals in which sTnC is expressed in cardiac myocytes would be an important model system for finally resolving this issue.

Because the discussion of the role of cTnC in determining the Starling properties of cardiac muscle was limited to one paragraph of the review, it was impossible to cite all of the references concerning this controversy. Accordingly, we cited what we thought were the most important and visible references from both Dr. Gulati and Dr. Moss’s groups. We are gratified that our review has stimulated further discussion of this important scientific problem. Given the interest in this area, it seems likely that the role of cTnC in determining the Starling properties of cardiac muscle will soon be clear.

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New Criteria for Diagnosis of Regular, Wide-Complex Tachycardias
We read with great interest the recent article by Brugada et al1 outlining new electrocardiographic criteria for the differential diagnosis of regular, wide-complex tachycardias. We note that the authors studied their subjects in the drug-free state, and thus the application of the new parameters to patients receiving antiarrhythmic drugs remains uncertain. Because many patients presenting with wide-complex tachycardia are receiving antiarrhythmic agents, it is important to determine whether the Brugada criteria can accurately diagnose the site of origin of the arrhythmia in these cases.

Class IC antiarrhythmic agents, although in deep disrepute for the treatment of ventricular arrhythmias, have been shown to be effective in the prevention of recurrent atrial fibrillation.2 However, as pointed out by several authors,3–6 a proportion of patients with atrial fibrillation treated with IC agents may develop atrial flutter with 1:1 conduction associated with a wide QRS complex. Under these circumstances, the differential diagnosis between supraventricular and ventricular tachycardia can be difficult.3–6 To determine whether the Brugada criteria could be applied to type IC–induced widening of supraventricular tachycardias, we reviewed the 12-lead electrocardiograms from five published cases7–9 and one case of our own in whom therapy with IC agents for supraventricular arrhythmias resulted in a regular, wide-complex tachycardia and in whom the diagnosis of supraventricular tachycardia with aberration had been established. Application of the commonly used criteria of Wellens10 resulted in five traces being interpreted as ventricular tachycardia and in one inconclusive interpretation. In contrast, analysis by the new criteria correctly identified the arrhythmias as being supraventricular in origin in five cases and incorrectly as ventricular tachycardia in one.9