Correspondence

Letters to the Editor must not exceed 400 words in length and may be subject to editing or abridgment. Letters must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Only some letters will be published. Authors of those selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication.

Diagnosis of Constrictive Pericarditis
To The Editor:

The interesting case featured in “Images in Cardiovascular Medicine” in the March 3, 1998, issue of Circulation1 illustrates how elusive the diagnosis of constrictive pericarditis can be and demonstrates how important it is to perform a comprehensive 2-dimensional/Doppler echocardiographic examination on all patients referred to the echocardiography laboratory. In patients with symptoms and signs of congestive heart failure, it does not suffice to simply report on the systolic function of the left and right ventricles. Comprehensive evaluation should include assessment of diastolic function. Likewise, a comprehensive invasive evaluation, if needed, should not be limited to the nonspecific findings of a dip-and-plateau waveform and equalization of elevated ventricular diastolic pressures but should include an assessment of ventricular interdependence.2

Two-dimensional echocardiographic features suggestive of constrictive pericarditis, namely, abnormal motion of the interventricular septum and a dilated inferior vena cava, should prompt serious consideration of this diagnosis. Using pulsed-wave Doppler to assess diastolic filling, the echocardiographer can provide confirmatory evidence of constrictive pericarditis by demonstrating respiration-related changes in the mitral and tricuspid inflow velocities and in pulmonary vein and hepatic vein flow.2,3

The traditional criteria used for the invasive diagnosis of constrictive pericarditis have been shown to be nonspecific.4 Simultaneous right and left heart catheterization should include an assessment of the dynamic changes in intracardiac pressures that occur with respiration. Right and left ventricular systolic pressure changes are discordant in constrictive pericarditis because there is increased ventricular interdependence; these discordant changes are highly predictive of constrictive pericarditis.4

The decrease in the right ventricular diastolic pressure seen after pericardectomy (Figure 1 of the March 3 case) reminds us that constrictive pericarditis is eminently treatable and should always be considered in the differential diagnosis of patients presenting with congestive heart failure, especially if ventricular systolic function is normal.

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Response
We appreciate the thoughtful comments of Drs McCully, Higano, and Oh regarding our image, “Constrictive Pericarditis” (Circulation. 1998;97:806). We, of course, agree that in patients with congestive heart failure, echocardiographic evaluation (and invasive study, when indicated) should be thorough, as they describe. As they note, multiple abnormalities suggestive of constrictive pericarditis can be seen on both M-mode and 2-dimensional echocardiography. The specific abnormalities they describe are highly valuable for detecting constrictive pericarditis, and the simultaneous presence of several of these abnormalities strongly supports the diagnosis. We chose to illustrate certain clinical findings pointing to this diagnosis and the confirmatory evidence of CT, which is more useful than echocardiography for quantifying pericardial thickness.

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Splice Mutations in KVLQT1?
To The Editor:

Li et al1 propose that 2 new mutations in KVLQT1 in Romano-Ward syndrome (RWS) disrupt splicing, leading to frameshift and premature protein truncation, acting through a loss-of-function mechanism. This is surprising because missense mutations in KVLQT1, acting in a dominant-negative manner, predominate in RWS. In Table 2 of the article by Li et al, 24 of the 26 mutations are missense (the 2 remaining being discussed here). We suggest alternative interpretations.

The SP/A249/g-a mutation is a substitution G to A at the third position of codon 249, in which GCC is altered to GCA, occurring at the donor splice junction of exon 6. Mutation of splice sites can cause skipping of the affected exon, activation of cryptic splice sites, or retention of the intron.3 Exon skipping is common. If this occurs in SP/A249/g-a, the predicted protein will lack part of the pore and S6 transmembrane domain but may still multimerise, because if exon 6 is skipped, the resulting mRNA would still read “in frame.” In-frame but deleted transcripts may be stable and translated into protein, as shown for the dystrophin gene.3 The effect of the mutation should be confirmed in RNA, because frameshift and premature truncation of the KVLQT1 protein, as suggested by Li et al, would be a truly novel type of KVLQT1 mutation in RWS.

The second mutation is the 3-bp deletion across an exon/intron boundary (denoted SP/V212/ΔGGT), disrupting the 5′ donor site of exon 5. A donor consensus splice site consists of CAG.gtaagt.4 In the patient in the study by Li et al, the wild-type exonic sequence GGG.TGT.gtaagt is mutated to GGG.GTaagt by deletion of 3 nucleotides, Gtg. The authors propose that the mutation SP/V212/ΔGGT alters splicing, leading to a 1-bp deletion in the coding region, causing frameshift and premature truncation of the predicted protein (see Figure).

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However, a potential splice sequence, GGG-gtaagt, remains.4 Splicing here would delete a single valine,5 causing a mutant protein capable of dominant-negative action.

Missense mutations in KVLQT1 predominate in RWS, whereas nonsense and frameshift mutations predominate in Jervell and Lange-Nielsen syndrome (Tyson, 1998, unpublished data). Carriers of nonsense mutations rarely manifest RWS clinically. The gene product of the null allele should not interfere with the wild-type allele in a dominant-negative manner.

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Goals for Cholesterol Lowering

To The Editor:

The editorial by Professor Grundy1 on the statin trials has prompted this letter, which is based on personal observations on treatment of atherosclerotic ischemic heart disease2 that has reduced non-HDL to “subnormal” levels and halted atherosclerosis.

Professor Grundy’s editorial3 on the 3 major statin trials has failed to resolve the question of how low LDL should be reduced to have the maximum effect in halting atherosclerosis.

It is now accepted that the severity of atherosclerosis is related to the LDL level. However, at any particular level, the degree of atherosclerosis can vary enormously.4 The study by Cullen and Assmann5 implicates a factor, probably inherited, possibly located in vascular endothelium and/or the platelets but perhaps elsewhere, that augments the atherogenic action of LDL and that, for convenience, I have called the coronary atherosclerotic index (CAI).

Those individuals with a high CAI would be prone to develop atherosclerosis when LDL levels might be considered normal and would correspond to Grundy’s Figure 2, linear model A; those with moderate CAI to Figure 2, curvilinear model C; and those with low CAI to Figure 2, threshold model B. A consideration of the statin trials would show that most of the patients in the WOSCAPS trial would have a low CAI and thus be expected to have a threshold for LDL. However, in the CARE and 4S trials, a small proportion of patients with a high CAI would be diluted with a larger proportion of patients with moderate and low CAIs, and the results would thus be confounded. It would be instructive to stratify patients in the CARE and 4S trials into the 3 CAI groups and to compare risks with LDL levels. It would also be interesting to compare the relative risks of maintaining 1 group of patients with a high CAI at a mean LDL level <2.0 mmol/L with a similar group maintained at <3.0 mmol/L.

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QT and Dispersion of Ventricular Repolarization: The Greatest Fallacy in Electrocardiography in the 1990s

To The Editor:

The recent, most thoughtful editorial authored by Coumel et al,1 commenting on the article by Zabel et al,2 is likely to create a great deal of interest and perhaps also some controversy. The arguments presented challenge the prevailing interpretation of the meaning of QT dispersion.

As the authors point out, there is only 1 end of repolarization in body surface ECGs, generated by source events in the myocardial region repolarizing last. This argument holds because there are no significant nondipolar components during repolarization in surface ECG leads. The apparent QT dispersion is due to differing spatial orientation of the ECG lead vectors and their differing sensitivity, which modifies T-wave amplitudes even if the projections of cardiac vectors on them are identical otherwise. For true dispersion of repolarization, we also need to consider the onset of ventricular repolarization. In local epicardial electrograms, the best estimate of this time point is the maximum of the first time derivative, near T-wave peak. This is not at the end of the T wave in body surface leads. Exactly where it is remains to be seen. Has all this work on dispersion of repolarization focused on the wrong measurement?

Information about abnormal repolarization can be more readily extracted in the amplitude rather than time domain of the T wave. QT dispersion, as measured presently, does not relate to any electrophysiologically meaningful source events.

Indeed, the prevailing interpretation of QT dispersion seems to have an element of a great fallacy. Is this at least in part because our young generation of electrocardiographers is no longer adequately exposed to elementary concepts of vectorcardiography?

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**Significance of Soluble P-Selectin, Von Willebrand Factor, and Other Adhesion Molecules in Hypercholesterolemia and Peripheral Artery Disease**

*To The Editor:*

We recently read with interest the paper by Davì and colleagues,1 who reported raised levels of both soluble P-selectin and von Willebrand factor in the plasma of 20 patients with hypercholesterolemia compared with 20 normocholesterolemic controls, with a strong (P = 0.0001) correlation between the molecules. We are delighted that they have confirmed our previous and recent observations of raised levels of von Willebrand factor among patients with this risk factor.2 However, we are unable to confirm their finding of raised soluble P-selectin in hypercholesterolemia in a cross-sectional study of similar population and design.3 The reasons for this difference are unclear but are unlikely to be simply related to the use of different reagents than those of Davì and colleagues.1

Davì and colleagues1 hypothesize that circulating levels of P-selectin may represent, in this clinical setting, an in vitro marker of endothelial cell and/or platelet activation. We beg to differ. It has been hypothesized that soluble P-selectin is a marker of platelet activation and does not appear to represent endothelial cell activation.4,5 In support of this concept, it can be noted that the administration of DDAVP (desmopressin, a substance that stimulates the endothelium) to healthy subjects results in increased levels of von Willebrand factor but no change in levels of soluble P-selectin in the plasma.6 Thrombocytosis is often present in cardiovascular disease, so that a platelet count should be included because it correlates with levels of soluble P-selectin.7 Furthermore, several groups have been unable to correlate levels of von Willebrand factor (probably the “gold standard” in vivo marker of endothelial cell activation and damage) with those of soluble P-selectin in various studies that have included patients with diabetes, thrombocytophenia purpura, hypertension, and atherosclerosis.

Therefore, in order for the study of these molecules to provide something of substance, we feel that a consensus needs to be achieved. Until several large, hopefully prospective, comparative studies are published, it seems likely that the routine measurement of soluble adhesion molecules has little to offer practicing physicians toward attaining their goal of improving patient care. Additional studies may tell us if the measurement of soluble adhesion molecules will have more concrete answers to offer rather than simply asking more questions and offering inconsistencies.

**Response**

We thank Dr Blann and colleagues for their interesting comments on our article.

Unfortunately, we don’t have a clear explanation for the apparent discrepancy between some of our results and data from his group, but we agree that it should not be related to the reagent source.

Dr Blann and colleagues propose that soluble P-selectin should rather be considered a marker of platelet activation. It is also our opinion that plasma P-selectin may reflect platelet activation, and recently we have described a significant correlation between levels of soluble P-selectin and urinary 11-dehydro-TXB2, an established marker of in vivo platelet activation, in hypercholesterolemia (M. Romano, MD, et al, unpublished data). However, we believe that more convincing evidence should be obtained to completely rule out the contribution of a dysfunctional endothelium to circulating P-selectin levels.

We think that definitive conclusions cannot be drawn from studies with DDAVP administration to healthy subjects because they may not be directly applicable to patients with vascular damage. It is known that when endothelial cells are exposed to various stimuli, von Willebrand factor (vWF) and P-selectin are mobilized from Weibel-Palade bodies to different compartments: vWF is mainly released, whereas P-selectin remains bound to the cell surface.8 DDAVP also induces P-selectin translocation to the endothelial cell plasma membrane.9 Thus, it can be predicted that DDAVP administration may determine an increase in plasma vWF without modifying soluble P-selectin.

However, an altered endothelium may behave differently. In particular, the endothelium overlying atherosclerotic plaques overexpresses P-selectin3 and is likely to be subjected to interactions with inflammatory cells and exposure to inflammatory mediators, eg, cytokines and proteolytic enzymes, that might induce P-selectin release. In pathological conditions, then, P-selectin and vWF may undergo different mechanisms of release, and this might explain why it is not always possible to observe a clear correlation between vWF and soluble P-selectin levels. This would imply that vWF and P-selectin may monitor different aspects of the functional status of the endothelium.

Therefore, although our current knowledge may suggest that platelets represent the principal source of soluble P-selectin under physiological conditions, it cannot be excluded that an altered endothelium might also contribute to increases in P-selectin levels in selected pathological states. The extent and relevance of this contribution and therefore the specificity of P-selectin as an endothelial index remain to be established, and we agree with Dr Blann and colleagues that additional studies are needed to provide consistent criteria for a correct evaluation of circulating adhesion molecule measurements.

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Splice Mutations in KVLQTI?
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