Our own findings indicate an increase in Vc/Dm ratio as the most characteristic abnormality in patients with mitral valve disease. In the accompanying figure Vc has been plotted against Dm in different clinical situations including 19 patients with mitral valve disease. Isopleths of Dlco which follow a rectangular hyperbola have been constructed assuming 1/Dm = 1.263. Eighteen of the 19 patients with mitral valve disease have a ratio > 3 which is more than the ratio in all the 18 normal subjects. These estimations were performed by a steady state technique, the details of which have been described earlier.

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References


The author replies:

To the Editor:

The observations of Drs. Pande, Gupta and Guleria are limited to measurements of the subdivisions of the diffusing capacity in patients with mitral valve disease. This is a minor point of my article. Estimations of Dm and Vc are based on the measurement of Dco at different inspired oxygen tensions and the graphical solution of Roughton and Forster's equation. As a result, values obtained for these subdivisions are considerably less reliable than the total Dco. One should not draw conclusions from variations in Dm and Vc when the Dco is normal. An increase in inspired oxygen tension in patients with mitral valve disease probably produces physiological changes in the pulmonary capillary bed. This casts further doubt on the interpretation of Dm and Vc.

The major point of the above letter is their finding of a low Dm and therefore increased Dm/Vc ratio in patients with mitral valve disease. However, Dm is a less reliable measurement than Vc, especially when the pulmonary capillary blood volume is small. In the latter case the slope of the line for the graphical solution for Dm and Vc is steep. The intercept on the y axis is then less certain and Dm varies widely. It may approach infinity when Vc is very low indicating that the capillary resistance to diffusion predominates. This explains the rather high values for Dm that I reported.

Dco measurements are clinically useful in patients with mitral valve disease and other pulmonary circulatory disorders. Measurements of the subdivisions do not provide further information of clinical value. For the reasons stated above, I do not believe that values obtained for Dm in these patients are very meaningful physiologically. Conclusions regarding capillary geometry based on changes in Dm and a Vc/Dm ratio in patients are unreliable. The subdivisions of the Dco are conceptually useful, but interpretation of the total Dco is on much firmer ground.

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Reference


Sleep and Ventricular Premature Beats

To the Editor:

We were pleased by the results reported by Lown and his colleagues (Circulation 48: 691, 1973) regarding the importance of neural mechanisms to the ventricular ectopic activity seen in some patients. Their suggestion that neural events might trigger ventricular extrasystoles in patients is substantiated by experimental studies in animals. We as well as others have shown that electrical stimulation of brain centers will produce a variety of cardiac arrhythmias. The same is true when peripheral autonomic nerves are stimulated. Furthermore, circumstances that give rise to arrhythmias such as digitalis administration and experimental myocardial infarction produce generalized excitation of brain stem nuclei. Depression of these brain sites by neurodepressant drugs or surgical removal delays and even corrects these arrhythmias.

The animal data suggest that enhanced sympathetic tone is the causative factor in disrupting cardiac rhythm. But as pointed out by Lown and colleagues, "it is hard to account for the failure of large doses of propranolol to reduce VPBs in three patients, though such a result was observed with sleep alone." This seeming paradox becomes clear when one considers the results of Randall and colleagues. They have shown that electrical stimulation of cardiac sympathetic nerves produces arrhythmias which cannot be prevented by pretreating animals with propranolol. Additionally, it was shown that the arrhythmias could not be blocked by atropine. Thus, arrhythmogenic stimuli from the CNS may travel to the heart through nerves whose neuroeffector junctions are not amenable to blockade by conventionally employed antagonists.

Lown and colleagues put forward the view that "the pharmacologic focus should be in restraining the neurophysiologic trigger rather than in attempting to protect the cardiac target." This is an approach that we have been advocating for several years. For example, we have found that several of the drugs currently in use for treating arrhythmias possess neurodepressant actions. Furthermore,
we have attempted to discover new and better antiarrhythmic drugs by testing drugs with known 
neurodepressant effects against experimentally induced 
arrhythmias.3 We have found that chlordiazepoxide is effective 
in the treatment of ventricular arrhythmias induced by 
either digitalis or coronary occlusion. Chlordiazepoxide in 
combination with the peripherally-acting antiarrhythmic 
agent, lidocaine, is able to enhance the effect of lidocaine on 
arrhythmias evoked by coronary occlusion.4

Attacking the "neurophysiologic trigger" with drugs has 
also been reported by Nixon and colleagues in patients.5 
They suggested that prophylactic use of sleep therapy (i.e. 
petridine plus promethazine) reduces mortality from acute 
myocardial infarction.

Most methods for finding new antiarrhythmic drugs have 
been based on the idea that drugs must act directly on 
myocardial cell membranes to exert an antiarrhythmic 
effect. The failure of studies on isolated tissues to lead to 
proposing new drugs may be due to the fact that the 
causative factors of arrhythmias occurring in vitro are missing 
in these preparations. Based on the data cited above plus 
the data of Lown and colleagues showing that sleep will 
suppress ventricular premature beats, we feel that consideration 
of the nervous system may provide the basic understanding 
for discovering safe and effective new antiarrhythmic drugs.

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Propranolol and Oxygen-
Hemoglobin Equilibrium

To the Editor:

The article by Lichtman and others (Circulation 49: 881, 
1974) entitled "Effect of Propranolol on Oxygen Binding to 
Hemoglobin in Vitro and in Vivo" was a major step forward 
in the understanding of the biochemical effects of this drug.

We would disagree, however, with one of the conclusions. 
The authors state that "Propranolol (10 to 360 mg) ad-
mittted to human subjects did not affect hemoglobin-
oxgen affinity." This was based on measurement of P50 
in six presumably healthy subjects before propranolol, and four 
and twenty-four hours after administration of forty 
milligrams or less. The authors found no significant change 
in P50. They also measured P50 in two subjects on large doses 
(180 and 360 mg per day) of propranolol and found it to be 
"within one standard deviation of their normal mean."

We have shown that patients with coronary artery disease 
on chronic oral therapy with propranolol (mean 150 mg per 
day) for at least three months do have a significantly 
increased P50 on the drug compared to their P50 off the drug 
(Am J Cardiol 33: 170, 1974). This demonstrated shift in 
oxgen affinity could increase systemic oxygen delivery 
20-30%.

Perhaps the differences in our data may be explained by 
differences in duration of drug ingestion. Most patients in 
Lichtman's paper were studied after only one dose of the 
drug. The two patients that were on chronic oral therapy, 
only had measurements while they were on propranolol. No 
control P50s were done while they were off the drug.

The duration and amount of oral therapy necessary for the 
in vivo effect of propranolol on P50 is incompletely un-
derstood. Manchester and others have shown observable 
effects on P50 2 hours after 40 mg of propranolol given as 10 
mg orally q4h (Manchester et al., Circulation 45: (suppl II): 
11-109, 1972). We have shown that patients on chronic oral 
therapy with propranolol, when compared to themselves off 
the drug as controls, do have an increase in P50. Studies to 
elucidate the time course of this effect of the drug are 
underway.

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The authors reply:

To the Editor:

We thank Dr. Sheps and colleagues for calling our attention 
to their studies and for their comments. Their finding 
that propranolol results in an increase in P50 after at least 
three months of treatment is of interest but the abstract by 
Schrumpf et al. to which they refer does not indicate a direct 
effect of propranolol on the red cell. Propranolol used in 
higher doses for long periods may lead to changes in cardiac 
or pulmonary function which might result in an increase in 
P50 indirectly.

At this time four variables are accepted as capable of 
producing major alterations in the oxygen-hemoglobin 
equilibrium: red cell temperature, red cell 2,3-
diphosphoglycerate (2,3-DPG) concentration, red cell pH 
and the non-pH related effect of red cell CO2. When P50 is 
measured at standard conditions, all but 2,3-DPG are nor-
malized. P50 at standard conditions (P50 std), which we 
assume to have been the variable measured by Schrumpf et 
al., is usually, therefore, an indirect measure of red cell 2,3-
DPG if the red cell contains normal adult hemoglobin. Red 
cell 2,3-DPG concentration has been correlated most con-
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