Effects of Digitalis on the Exercise Electrocardiogram

Tonkon and his colleagues (see page 714) have partially clarified the analysis of exercise testing in patients who are receiving digoxin. This was done by showing that certain depressions of the J junction, sometimes accompanied by flat or upward-sloping ST-segment depressions, are not associated with any current abnormality of the coronary arteries. The ST-segment changes in these subjects were modest. More pronounced ST-segment depressions may be a source of confusion for clinicians.

The report by Tonkon et al is an expansion of the approach provided by Friessinger and his colleagues. They analyzed “vasoregulatory” effects on the postexercise electrocardiogram in people who did not develop coronary disease in the three years following the test. As with the effects caused by administration of digoxin, these responses usually occur during exercise and remit with continued exercise. This characteristic is to be contrasted with other conditions which cause ST-segment depression in the absence of coronary arterial disease, such as valvular heart disease, hypertension, and left ventricular hypertrophy. In these conditions, the ST-segment depression can persist or worsen with continuing exercise. It is postulated that “vasoregulatory” is the appropriate term to describe the presumed altered autonomic response to stress in these patients.

Nevertheless, in contrast to the vasoregulatory response, the effect of administration of digoxin on the ECG does not occur at the onset of exercise. The fact that the onset is delayed somewhat after the start of exercise is similar to the “walk-through” phenomenon. The basis for the ST-segment depression in this process is not well understood but may be due to a unique adaptive response of the peripheral neurovasculature. Tonkon and coauthors have drawn attention to their unanswered question about the mechanism of the effect of administration of digoxin on the exercise ECG.

Another unanswered question relates to whether administration of digoxin confuses the exercise ECG used for prognosis. Tonkon et al do not provide follow-up data regarding future coronary events in their subjects. Although unlikely, it is possible for people with normal coronary arteriograms to develop clinical ischemic coronary disease. It is widely recognized that ST-segment depression has a relationship to both current cardiac anatomy and future cardiac events. The report by Tonkon et al has dealt with only the former.

The subjects analyzed in this study by Tonkon and associates had no evidence for clinical heart disease. Digoxin was given for only experimental purposes. Although by no means certain, it may not be possible to apply the findings of their report to patients who need therapy with digoxin for treatment of arrhythmias or for heart failure due to myocardial or valvular disease but who do not have coronary arterial disease.

This report by Tonkon et al has provided a valuable contribution to the technique of exercise electrocardiography. The study has eliminated one problem raised by the use of digoxin and has brought into focus other questions pertinent for further study.

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References
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Colloid Osmotic Pressure and Pulmonary Edema

The flow-directed Swan-Ganz pulmonary arterial catheter has been a major asset for assessment of the hemodynamic status of the critically ill patient. Measurement of pulmonary arterial and pulmonary arterial wedge pressures provides quantitation of both left ventricular filling pressure and pulmonary microvascular hydrostatic pressure and, in turn, an estimate of left ventricular function and the risk of pulmonary edema; however, the classic Starling equation, which defines the transport of fluid across capillaries, takes five factors into account which, in addition to the microvascular (capillary) hydrostatic pressure, include (1) the perimicrovascular (interstitial) hydrostatic pressure, (2) the colloid osmotic (or oncotic) pressure of plasma, (3) the colloid osmotic pressure of the interstitial fluid, (4) the conductance of the fluid (coefficient of filtration) across the membrane, and (5) the coefficient of reflection, which quantitates the extent to which the semipermeable endothelial membrane prevents the egress of protein solute from the capillary. With the availability of practical methods for the clinical measurement of colloid osmotic pressure in plasma or serum, it is now possible to take into account an additional variable that determines the transport of fluid across the pulmonary capillary and, hence, the likelihood of pulmonary edema.

The pulmonary microcirculation, in contrast to the systemic microcirculation, has unique characteristics that serve to keep the interstitium and alveoli free of fluid. Since the normal colloid osmotic pressure of the upright human subject is 25 mm Hg and since the normal pulmonary microvascular pressure is approximately 8 mm Hg, there is a gradient of approximately 17 mm Hg that opposes the egress of fluid into the interstitial space. When the microvascular hydrostatic pressure is increased (as it is in instances of left ventricular failure), pulmonary edema appears when this hydrostatic pressure increases to levels that exceed the safety provided by the higher colloid osmotic pressure. The Starling transport equation would further predict that a critical reduction in colloid osmotic pressure of plasma may be followed by pulmonary edema, even though there is no substantive increase in microvascular hydrostatic pressure.

In attributing edema to an increase in hydrostatic pressure or to a lowering of oncotic pressure, we do so with the assumption that the permeability of the membrane (i.e., the coefficients of filtration and reflection) are not altered; however, in matter of fact, the structure and function of the microvascular membrane may be grossly impaired, and increased permeability is a third cause of pulmonary edema. Bacterial pneumonitis, aspiration pneumonia, heroin intoxication, inhalation of phosgene, and, experimentally, gram-negative microorganisms, histamine, alloxan, ozone, and the chelating agent, edetic acid (EDTA), have been implicated as causes of pulmonary edema due to altered permeability.

In addition to the hydrostatic defects, oncotic defects, and defects in permeability which may account for pulmonary edema, Staub, in a series of elegant experiments, has pointed to the dynamic flux of fluid provided by lymphatic clearance of extravascular fluid from the lung. Although the static forces defined in the Starling equation are operative, the clearance of fluid from the interstitium by the lymphatic system constitutes an additional dynamic variable that ultimately determines sequestration of fluid into the lung. Studies by Brigham and Owen have also demonstrated another safety factor. When pulmonary microvascular pressure is increased, the flow of lymph not only increases, but the oncotic pressure of the lymph, which is believed to be representative of interstitial fluid, also decreases. This further reduces the oncotic forces which would favor egress of fluid from the pulmonary capillary.

It is within this context that we comment on recent investigations on the clinical measurement of colloid osmotic pressure and most especially the article by Rackow and associates (see page 709). Fundamental to such clinical studies has been the availability of a practical device for routine measurement of colloid osmotic pressure. As little as 50 μl of lightly heparinized plasma or serum suffice for this technically simple measurement, which may be completed within two minutes.

In confirmation of prior studies by our group, Rackow and his collaborators observed a close relationship between pulmonary edema and the colloid-hydrostatic pressure gradient. Accordingly, when the measured pulmonary arterial wedge pressure was subtracted from the colloid osmotic pressure and this difference was less than 4 mm Hg, pulmonary edema inevitably appeared. The net intravascular driving pressure, which represents the difference between the plasma colloid osmotic and pulmonary microvascular hydrostatic pressures, emerges as a particularly useful quantitation with which the predictability of the risk of pulmonary edema is improved.