Monitoring Cardiovascular Disease Progression

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Background

Cardiovascular disease management guidelines and therapeutic trials are traditionally driven by efforts to reduce morbid events over a finite period of time, often the 10-year outcome that forms the basis for most algorithms aimed at defining risk [1,2]. This relatively short interval in a person’s life mandates that trials focus on advanced disease with high short-term morbidity that will make it possible to identify a favorable effect of an intervention. This restriction makes it impractical to study early disease, when an intervention might be dramatically effective in prolonging life but will have too few morbid events over 5 or 10-year period of time to demonstrate effectiveness of therapy. A proposed solution to this problem is to aim therapy not exclusively at morbidity reduction but rather at disease progression which should be a forerunner of morbid events. We have been utilizing a non-invasive evaluation program in our centers in Minneapolis, MN and Sarasota, FL over the past 20 years (Minneapolis) and 10 years (Sarasota) in order to identify early disease in need of treatment and to track disease severity to monitor progression. Our experience has convinced us that early vascular or cardiac disease detection is of great value in detecting, monitoring and treating cardiovascular disease [3].

Methodology

The goal of early detection is to identify functional and structural abnormalities of the arterial vasculature and left ventricle which identify early disease that may progress to future morbid events [4,5]. The tests of function and structure we utilize are noninvasive and non-radiating and can be completed in one room in one hour. They are aimed at detecting abnormalities of the small microvascular arteries, the large conduit arteries and the left ventricle. The underlying concept is that most cardiovascular morbid events are complications of structural or functional abnormalities in these organ systems.

The tests include the following 10 measurements [5]: 1. Resting, sitting blood pressure; 2. Pulse-contour analysis to calculate small artery compliance [6]; 3. Pulse-contour analysis to calculate large artery compliance [6]; 4. Optic fundus photography to evaluate the microvasculature; 5. Carotid ultrasound to evaluate wall thickness and plaque formation; 6. Urine specimen for microalbumin/creatinine ratio; 7. Blood pressure response to 3-minutes of mild treadmill exercise; 8. An electrocardiogram; 9. Left ventricular ultrasound for LV mass and chamber dimension; 10. A blood sample for NT-pro BNP. All 10 tests are individually graded as normal (0), borderline (+1) and abnormal (+2), with age and gender adjustment for ultrasound measurements. Both centers noted that using the total score of the 10 tests of 0-2, 3-5 and 6+ divided the population into nearly equal one-thirds. Therefore, those subgroups have been identified, respectively, as no disease, early disease and advanced disease.

Morbid events vs. disease progression

Most morbid events themselves may be precipitated by dramatic complications of cardiovascular disease, such as clots, ruptures or cardiac rhythm disorders. Nevertheless, these complications occur in the setting of advanced functional or structural abnormalities of the arteries or left ventricle. Preliminary outcome data demonstrate that those individuals without structural or functional abnormalities have a very low incidence of future morbid
events and that the severity of the abnormalities is directly related to the future risk [6]. The clinical experience in this referred or self-referred asymptomatic adults in our two separate populations demonstrate that about one-third are free of abnormalities, one-third have mild or early abnormalities and one-third advanced abnormalities. If the latter subgroup were placed on preventive therapy, we might be treating one-third of the adult population, which would be consistent with the data on cardiovascular morbid events in the American population. These data raise the possibility that disease progression might serve as a substitute for morbid events to test the effectiveness of therapy aimed at preventing morbid events in an asymptomatic population.

Effect of therapy

The traditional approach to documenting the efficacy of therapy is to mount a large prospective trial powered to demonstrate a significant reduction in morbid events, over an interval long enough for adequate morbid events, to occur so that the intervention group can be demonstrated to have fewer events than the non-intervention group. This approach has required studying populations with a high near-term risk of a morbid event. If disease progression could be utilized as a substitute for events, far smaller trials over shorter intervals in individuals with early disease might be possible.

We have undertaken three intervention trials of drug therapy in the early stage of disease that provides encouraging evidence that such an approach is feasible [7-9]. This approach needs further documentation so that regulatory bodies may accept disease progression as a suitable endpoint for effectiveness. Such a result would open the door for improved management of the early stages of cardiovascular disease and a population-wide prolongation of healthy life.

References