Published in final edited form as:

Congest Heart Fail. 2010 July ; 16(4): 139–140. doi:10.1111/j.1751-7133.2010.00155.x.

Heart Failure Risk: Lessons from the Family

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Importance of family history

Obtaining a family history is considered a core component of the initial clinical assessment in patients with heart failure (HF).¹ In general medical encounters, the family history has consistently been shown to be an effective risk assessment tool,^{2,3} even when assessing non-Mendelian or complex diseases. This is because an individual's family history incorporates information not only about the individual's heritable risk, but also about the shared environmental influences such as diet, lifestyle and other behaviors. Thus, a test as simple and inexpensive as ascertainment of family history may represent an integrated measure of genetic and environmental risk in the context of predisposition to HF.

HF as a chronic progressive disorder and complex genetic trait

In addition to family history, current HF guidelines by the American College of Cardiology/American Heart Association (ACC/AHA)¹ also recommend that HF be considered a progressive condition with four stages (A–D). Stage A represents persons with cardiovascular risk factors, such as hypertension, diabetes or obesity, but without cardiac structural changes or symptoms. In stage B HF, cardiac structural changes, such as left ventricular (LV) hypertrophy or remodeling, are present but patients remain asymptomatic. When overt symptoms of HF are present, patients are considered to be in stage C, which then progresses to terminal or end-stage (stage D) disease.

By and far, the etiology of HF in the community relates to common, chronic cardiovascular conditions (such as hypertension, diabetes or coronary heart disease), rather than to single gene mutations (as in dilated or hypertrophic cardiomyopathies). In latter cases, HF is regarded as a monogenic disorder, where rare, disease-causing genes exert large effects, and HF may exhibit a Mendelian pattern of inheritance.⁴ In this commentary we will focus on the former scenario, where HF is regarded as a complex genetic disease with multiple, common genetic variants and shared familial factors contributing to overall disease susceptibility. In these cases, familial clustering of HF involves a complex interplay of heritable risks and environmental factors that can contribute to HF at all stages of the disorder. We will consider the familial risk of HF within the framework of the ACC/AHA classification system, from the risk of known cardiovascular risk factors (stage A), to that of LV remodeling (stage B) and the overt clinical syndrome (stage C).

Family history in patients with HF risk factors (HF Stage A)

Several studies have demonstrated the contribution of family history to the risk of cardiovascular conditions in stage A HF. In the Framingham Heart Study, 5209 adults and 5124 of their children have been followed since 1948⁵ and 1971⁶ respectively with detailed assessments for cardiovascular risk factors and disease. In this large two-generational sample, parental cardiovascular disease was associated with increased risk of future cardiovascular events in middle-aged offspring;⁷ while sibling cardiovascular disease conferred increased risk for future events beyond parental disease and established risk factors.⁸ Further, parental diabetes, obesity and metabolic syndrome were found to be associated with increased risk for type 2 diabetes in offspring.⁹

In the Atherosclerosis Risk in Communities (ARIC) Study of 15792 adults,¹⁰ the family risk score, comparing the age- and sex-specific incidence of disease in a family with that expected in the general population, was predictive of coronary heart disease¹⁰ as well as incident type 2 diabetes (along with a family history of diabetes).¹¹ Familial clustering of cardiometabolic risk factors was also shown in the National Heart, Lung, and Blood Institute's Family Heart Study,¹² where a family history of diabetes or hypertension was related to co-occurrence of impaired fasting glucose, hypertension and dyslipidemia, even among the non-obese. Similarly in the San Antonio Family Heart Study of 1236 individuals from 42 extended families, a family history of diabetes or hypertension was associated with a broad panel of cardiometabolic measures such as fasting glucose, body mass index, blood pressure, cholesterol and triglycerides.¹³ These investigators further found that behavioral factors (such as physical activity and diet) clustered within families.¹⁴

Family history in preclinical LV remodeling (HF Stage B)

Familial predisposition to LV hypertrophy was demonstrated in the MONItoring of trends and determinants in CArdiovascular disease (MONICA) study,¹⁵ where sibling LV hypertrophy was associated with increased prevalence of LV hypertrophy and concentric remodeling compared to unrelated members of the population. These findings are consistent with data in twins^{16–18} and in the general community¹⁹ showing the heritability of LV mass and wall thickness, as well as very recent genome-wide association studies²⁰ further revealing genetic factors underlying these traits.

Family history in overt HF (HF Stage C)

The association between parental HF and overt HF in offspring was demonstrated in the Framingham Heart Study.²¹ Having at least one parent with overt HF (occurring before the age of 75 years) increased the hazards of future HF in offspring by 70% (i.e. hazard ratio 1.70; 95% CI, 1.11–2.60). This association remained robust even after accounting for conventional cardiovascular risk factors (such as age, sex, blood pressure, body mass index, cholesterol, diabetes, previous myocardial infarction, valve disease and antihypertensive therapy), excluding participants with myocardial infarction or valve disease, and adjusting for LV mass. These observations suggest that the enhanced HF risk was not merely mediated by increased risk of stage A risk factors or stage B LV remodeling.

Integrating the stages of HF, this large two-generational sample of the Framingham Heart Study also provided evidence that parental HF was related cross-sectionally to greater burden of cardiovascular risk factors, enhanced odds of LV systolic dysfunction (multivariable-adjusted odds ratio 2.37; 95% CI, 1.22–4.61), and a trend to increased LV hypertrophy (odds ratio 1.35, 95% CI, 0.99–1.84) and LV dilation (odds ratio 1.29, 95% CI, 0.96–1.72) in offspring. Together with the demonstrated increased hazards of future HF in offspring, these data suggest an important role for familial factors in the progression of HF

from stage A risk factors, through stage B LV remodeling and dysfunction, to overt stage C HF in the community.

Conclusions

Familial factors have been shown to contribute to early and overt stages of HF. Obtaining a family history is therefore an integral component of current HF guidelines.¹ Ultimately, the goal of assessing family history would be to identify at risk persons for preventive strategies, and improve individual patient outcomes as well as overall population health. To achieve this, more research efforts are needed to evaluate the predictive value of family history and its potential impact on health outcomes, as highlighted in the recent statement from the National Institutes of Health.² Until such data are available, clinicians and patients alike would be wise to take heed of the lessons that families can teach us regarding the risk of HF.

Acknowledgments

This work was supported by NHLBI Contract N01-HC-25195; grant RO1HL93328 (RSV).

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