ORIGINAL ARTICLE

Heart Failure Etiology Is Usually Pluricausal Whether or Not There is Associated Coronary Disease

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Abstract

The heart failure syndrome (HF) has diverse etiologies. In a 22-year study of predictors of HF in 126,235 persons, we attempted to identify etiologic factors independent of associated coronary heart disease (CAD) in 2594 persons hospitalized for the condition. For this purpose, subjects were stratified according to whether CAD was present. Of the subjects, 60% had evidence for CAD (CAD-HF). Because we also wished to study HF predictors in subjects without associated CAD according to specific HF etiology, the paper records of the other 40% of subjects (non-CAD-HF) underwent a detailed review so that we could determine the apparent primary etiology and contributory factors. A random sample of all subjects with CAD-HF underwent a similar paper record review so that we could ascertain contributory factors. The primary etiology among the subjects with non-CAD-HF was categorized as systemic hypertension (HTN) in 354, valve disease in 110, cardiomyopathies (including alcoholic and idiopathic) in 93, other specific miscellaneous in 55, and primary etiology not evident (unclear) in 423. The unclear-group subjects generally had multiple probable contributing factors. In addition to the preponderant etiology in subjects with non-CAD-HF, the mean number of contributory factors was 1.5; among subjects with CAD-HF, the mean number of contributory factors was 1.9. Frequent additional factors, in both CAD-HF and non-CAD-HF, were HTN, diabetes mellitus, atrial fibrillation, and heavy alcohol consumption. These data show that primary HF etiology is often uncertain and that HF etiology is usually multifactorial, whether or not CAD is present.

Introduction

The heart failure (HF) syndrome has diverse etiologies, with comorbid conditions often contributing to HF development or recurrence.[1–5] Causes of HF have traditionally been classified by singular disease processes (eg, coronary artery disease [CAD], hypertension [HTN], valve disease), but clinicians understand the importance of dealing with all remediable factors.[1,4,6] The concept of multiple risk factors, well established for CAD, is increasingly being applied to primary and secondary HF prevention.[1,4,6]

Atherosclerotic CAD is considered the major cause of HF in developed countries.[3,4,6] Thus, established CAD risk factors, such as diabetes mellitus, HTN, smoking, and lipid abnormalities would be expected to predict HF associated with CAD.[6,7] In a study intended as an analysis of HF precursors in a large population, we sought to minimize the confounding problem introduced by the CAD relation, by separating analyses of predictors of HF associated with CAD (CAD-HF) and of HF not associated with CAD (non-CAD-HF). We also attempted stratification of subjects with non-CAD-HF by evident cause. The classification efforts proved their value by showing apparent disparate roles of alcohol in CAD-HF and non-CAD-HF.[8] Although the classification process was intended to be part of the infrastructure of the study and not a data endpoint, we were surprised by some of the results, especially the difficulty in assigning an evident cause in many subjects with non-CAD-HF. Because we believe that others might also benefit from the lessons we learned, we present our observations here. Our data strongly reinforce the wisdom of the multiple risk factor approach to HF etiology.

The concept of multiple risk factors, well established for CAD, is increasingly being applied to primary and secondary HF prevention.[1,4,6]

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Materials and Methods

Study Population and Data

The study protocols were approved by the Institutional Review Board of the Kaiser Permanente Medical Care Program. All subjects gave written informed consent for use of data. Baseline data for 1978 to 1985 were from health examination questionnaires completed by 126,235 members of a comprehensive prepaid health care program in San Francisco and Oakland, California. The examination[9] included self-classified ethnicity, health measurements, and queries about sociodemographic status, habits, and medical history.

HF Ascertainment

We screened Health Plan data for persons with ≥ 1 primary hospitalization discharge diagnosis of code 428 ("heart failure") from the *International Classification of Diseases, 9th Revision, Clinical Modification* through December 2000. This yielded a group of 2787 persons. Accepted as having CAD-HF without paper record review confirmation were 880 subjects with separate discharge diagnoses of acute myocardial infarction, a coronary intervention, or an angiogram showing occlusion of ≥ 50% diameter of at least one major vessel. All other records were reviewed for confirmation of HF, using the Framingham Heart Study HF criteria,[10] and for classification as CAD-HF or non-CAD-HF. We excluded 193 persons, mostly as not having HF. Of the remaining 2594, 60% (1559) were classified as having CAD-HF and 40% (1035) were classified as having non-CAD-HF.

We performed detailed review of all 1035 subjects with non-CAD-HF, attempting to identify a single probable preponderant HF etiology. Strict criteria for HF[8] were used for classification of preponderant etiology as HTN, valvular disease, various cardiomyopathies, etc. Attribution to idiopathic dilated cardiomyopathy required that there be no apparent preponderant cause or major factors. Alcoholic cardiomyopathy required evidence of heavy alcohol intake as the only potential major factor. If there were contributing factors but none seemed severe enough to be the cause of HF, the etiology was labeled unclear. Probable contributing factors in addition to the preponderant etiology were tabulated for the 1035 subjects with non-CAD-HF. For comparison with respect to contributory factors, we did a similar detailed review of a randomly selected subset (n = 263) of all subjects with CAD-HF.

When data were available (81% of subjects with a paper record review), we also classified subjects according to left ventricular (LV) systolic function. If an ejection fraction (EF) estimate was available (n = 670), it was used to stratify LV function as good (EF ≥ 50%), fair (EF = 35%–49%), or poor (EF < 35%). If an imaging study stated no EF, we used written subjective evaluations (n = 382) or fractional shortening data (n = 26).

Further details about methodology have been published.[8]

Table 1. Demographic traits of study population and subjects with heart failure with and without associated coronary artery disease

Group	Study group n (column %)	CAD-HF n (column %)	Non-CAD-HF n (column %)
Total	126,235 (100)	1559 (100)	1035 (100)
Men	55,658 (44.1)	874 (56.1)	460 (44.4)
Women	70,577 (55.9)	685 (43.9)	575 (55.6)
Age < 50 years	89,311 (70.7)	219 (14.0)	182 (17.6)
Age > 50 years	36,924 (29.3)	1340 (86.0)	853 (82.4)
Black	34,109 (27.0)	494 (31.7)	390 (37.7)
White	69,970 (55.4)	911 (58.4)	550 (53.1)
Hispanic	5655 (4.5)	39 (2.5)	29 (2.8)
Asian	13,467 (10.7)	90 (5.8)	51 (4.9)
Other	3084 (2 .4)	25 (1.6)	15 (1.5)
College graduate	45,406 (35.7)	282 (18.1)	175 (16.7)
Smoke ≥ 1 pack of cigarettes per day	11,530 (9.1)	187 (12.0)	113 (10.8)
Alcohol: 1 or 2 drinks/day	22,695 (17.8)	236 (15.1)	196 (18.9)
Alcohol: ≥ 3 drinks/day	10,192 (8.0)	116 (7.4)	108 (10.4)
BP > 149/90 mmHg	39,233 (30.1)	1,187 (76.1)	778 (74.0)
Total cholesterol in 4th quartile	31,705 (25.0[a])	854 (54.8)	423 (40.3)
Blood glucose in 4th quartile	29,250 (25.0[a])	873 (56.0)	488 (46.6)
4th quartile BMI (≥ 30 kg/m^2)	14,346 (11.3)	400 (19.2)	284 (26.9)

[a] Not all subjects had a record of a test; the percentage is of those with a test.
BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; HF = heart failure.

Table 2. Selected baseline traits of largest etiologic subgroups among subjects with non-CAD–associated heart failure

Study group (percentage of total)	HTN (n = 354) column %	Valve disease (n = 110) column %	CM (n = 93) column %	Unclear (n = 423) column %
Men (44)	39	39	48	50
Women (56)	61	61	52	50
Age < 50 years (71)	22	18	37	11
Black (27)	53	18	42	31
White (56)	36	66	45	61
College graduate (36)	11	21	16	19
Smoke ≥ 1 pack of cigarettes per day (9)	8	8	16	13
Alcohol: 1 or 2 drinks/day (18)	17	24	16	18
Alcohol: ≥ 3 drinks/day (8)	5	4	16	15
BP ≥ 149/90 mmHg (30)	85[a]	58	50	73
Total cholesterol in 4th quartile	40	35	44	40
Blood glucose in 4th quartile	51	35	34	48
BMI ≥ 30 kg/m^2 (11)	34	12	24	26

[a] Fifteen percent of persons were judged to have HF mostly because of HTN; they had a BP < 140/90 at the baseline examination, with other evidence of HTN.
BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CM = cardiomyopathy; HTN = hypertension.

Analytic Methods

Subjects were monitored until one of the following occurred: December 31, 2000, admission for HF at a Health Plan facility, or termination of Plan membership. The mean duration of follow-up was 14.4 years, yielding an estimated 1,820,200 person-years. Comparisons of proportions with individual underlying factors or combinations of factors entailed the use of c-square tests.

Results

Baseline Traits of Subjects with CAD-HF and Those with Non-CAD-HF

Persons with CAD-HF (vs non-CAD-HF) were more likely to be male, white, obese, and smokers but less likely to be college graduates or heavy drinkers (Table 1). Mean age at HF diagnosis was similar: 74.0 years for CAD-HF and 73.6 years for non-CAD-HF. Baseline HTN was present in approximately three quarters of both groups, but the highest quartile of total cholesterol and glucose levels were more prevalent in the CAD-HF group.

Baseline Traits of Etiologic Subgroups of Subjects with Non-CAD-HF

The preponderant HF etiology among subjects with non-CAD-HF (Table 2) was judged to be HTN in 354 (34%), valve disease in 110 (11%), cardiomyopathy in 93 (9%), and unclear in 423 (41%). The remaining 73 had other specific causes (eg, arrhythmia, infection, anemia). Among the 93 subjects with cardiomyopathy, 31 were judged to have alcoholic cardiomyopathy, 30 had other specific types, and 32 had idiopathic cardiomyopathy. Mean age at diagnosis was 72.6 years for those with HTN, 72.9 years for valve disease, 66.2 years for those with cardiomyopathy, and 76.3 years for the unclear group. Disproportionately represented were women in the HTN and valve disease groups and black persons in the HTN group. Smokers and heavy drinkers of alcohol were overrepresented in the cardiomyopathy and unclear groups, and persons with a high body mass index or high blood glucose level were overrepresented in the HTN group.

Contributing Factors

The subjects with CAD-HF averaged 1.9 factors in addition to CAD, making a total of 2.9 factors. Only 7% of those with CAD-HF had no additional factors, whereas 24% had ≥3. Subjects with non-CAD-HF averaged 1.5 factors in addition to the primary etiology, making a mean total of 2.5 probable factors; 20% of these had ≥3. Among unclear-group subjects, almost half (46%) had ≥3 factors. The small number of probable factors in the cardiomyopathy group (mean = 0.5) is a consequence of the exclusionary definitions of idiopathic dilated cardiomyopathy and alcoholic cardiomyopathy. The remaining subjects with cardiomyopathy, composed of several small groups (postpartum, infiltrative, hypertrophic), averaged 1.5 additional factors.

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The frequencies of probable factors (Table 3) indicate important roles for HTN, diabetes, and atrial fibrillation in both CAD-HF and non-CAD-HF. The prominent role of HTN in non-CAD-HF is revealed by adding the 354 subjects considered to have HTN as the preponderant etiology to the 403 others with HTN as a probable factor, making a total of 757 (73% of those with non-CAD-HF). The role of heavy alcohol drinking in non-CAD-HF is shown by the 31 subjects with alcoholic cardiomyopathy and many of the 167 with alcohol as a probable factor, making a possible total of 198 (19%). By definition, atrial fibrillation was considered a factor if present at the time of HF diagnosis.

LV Function Categories

Combining the subjects with CAD-HF and those with non-CAD-HF with LV function data, the mean number of factors in addition to the primary etiology in 430 subjects with good LV function was 1.53; in 268 with fair LV function, it was 1.62; and in 378 with poor LV function, it was 1.62. These differences are not statistically significant. When subjects with CAD-HF and those with non-CAD-HF with LV function data were studied separately, there were also no significant differences between those in the various LV function categories in the number of additional factors (data not shown).

Table 3. Probable HF factors in CAD-HF[a] and non-CAD-HF[b]

Trait[c]	CAD-HF (%)	Non-CAD-HF (%)	χ-square p value
Alone or in combination[c]			
Total n reviewed	263[a]	1,035[b]	—
HTN	78	38	<0.001
Diabetes mellitus	41	25	<0.001
Atrial fibrillation	24	30	0.04
Heavy alcohol	10	16	0.02
Valve disease	18	7	<0.001
Licit drugs	9	6	<0.001
Renal failure (creatinine > 2.0 mg/dL)	5	7	0.22
COPD	3	8	<0.001
Anemia (hemoglobin < 10 g/dL)	2	5	0.01
Cancer	0.4	3	0.02
Factor plus primary etiology (CAD-HF same as above)			
HTN	78	72	0.04
Heavy alcohol	10	19	<0.001
Combinations of ≥2 factors[c]			
HTN/diabetes	37	11	<0.001
HTN/atrial fibrillation	15	14	0.55
HTN/alcohol	7	11	0.06
Atrial fibrillation/diabetes	5	5	1.00
Atrial fibrillation/alcohol	4	5	0.52
Diabetes/alcohol	6	4	0.08
Atrial fibrillation/valve disease	5	3	0.07
Atrial fibrillation/COPD	18	3	0.28
HTN/valvular	14	4	<0.001
HTN/licit drug	7	2	<0.001

[a] Randomly selected from 1559 subjects with CAD-HF.

[b] Records of all subjects with non-CAD-HF were reviewed.

[c] In addition to CAD association for subjects with CAD-HF; in addition to primary etiology for subjects with non-CAD-HF, except for "all HTN" and "all heavy alcohol." Where not defined in the table, the etiology is a judgment from all available data. Other single factors with n ≥ 10 included bradycardia (n = 20), sleep apnea (n = 16), HIV (n = 10), and illicit drugs (n =.10)
CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HF = heart failure; HTN = hypertension.

Discussion

HF Etiology Is Often Uncertain

We anticipated difficulty in ascertaining a preponderant cause in some subjects with non-CAD-HF but were surprised that the unclear subgroup was the largest subgroup. Most subjects in the unclear group had multiple apparent HF factors but no factor appearing strong enough to be assigned a primary role. Although we cannot rule out some degree of subjectivity in our judgments, we attempted to assign primary etiology in subjects with non-CAD-HF to create etiologic categories. We cannot quantitate the likelihood that the 41% of those with non-CAD-HF judged unclear is an underestimate or an overestimate. Whatever the actual proportion of unclear etiologies might be, the finding clearly indicates a need for caution when determining a cause of HF.

We did not attempt to determine whether CAD association with HF meant CAD etiology. The presence of CAD seemed likely to ensure the predictive power of CAD risk factors. Causality of CAD for HF involves a more difficult judgment than presence of CAD. It is not uncommon for patients with severe CAD but no history or evidence of myocardial infarction to develop HF. If myocardial infarctions from CAD are the usual basis of HF, some subjects assigned to the CAD-HF group by our criteria of CAD association might have HF as a consequence of other factors.

HF Usually Has More Than One Probable Causative Factor

Both the subjects with non-CAD-HF and those with CAD-HF usually had more than one probable causative factor (Table 4). The importance of HTN, atrial fibrillation, and diabetes mellitus for both non-CAD-HF and CAD-HF and of heavy alcohol consumption in non-CAD-HF comes as no surprise (Table 3). The substantial prevalence of valvular disease in subjects with CAD-HF is noteworthy and may reflect the presence of similar risk factors for both.[11]

Diabetes May Be an HF Factor Independent of CAD

In view of the association of diabetes mellitus with vascular pathology and endothelial dysfunction,[12,13] undiagnosed atherosclerotic or microvascular CAD might explain the substantial apparent role of diabetes in non-CAD-HF. Additionally there may be an independent diabetes-specific cardiomyopathy. Reports suggest a disproportionate association of HF or LV dysfunction in persons with diabetes[12,13] or poor glycemic control.[14] The diabetic cardiomyopathy concept is further supported by evidence in patients with diabetes of myocyte glucolipotoxicity and various metabolic perturbations.[15]

Table 4. Number of contributory factors in non-CAD-HF and CAD-HF

HF association and preponderant non-CAD-HF etiology	No. of subjects	Additional probable factors				
		0	1	2	≥ 3	Mean
All non-CAD-HF	1035	233	325	285	210	1.5
HTN	354	117	157	58	22	1.0
Valvular disease	110	30	46	25	9	1.1
Cardiomyopathy[a]	93[a]	63[a]	16[a]	12[a]	2[a]	0.5[a]
Unclear	423	—	77	152	194	2.3
CAD-HF[b]	263[b]	19	68	112	64	1.9

[a] Includes 32 subjects with idiopathic dilated cardiomyopathy, defined as having no evident probable factors, and 31 subjects with alcoholic cardiomyopathy, defined as having no evident factors except heavy alcohol intake.
[b] Randomly selected from 1559 subjects with CAD-HF.
CAD = coronary artery disease; HF = heart failure; HTN = hypertension.

Strict Definitions Probably Reduce the Numbers in Some Categories

Exclusionary definitions resulted in small numbers of subjects with HF attributable to alcoholic or idiopathic dilated cardiomyopathy. Problems in defining these entities are well known.[16–18] Alcoholic cardiomyopathy is often subclinical,[18,19] and alcohol intake is often underestimated; some unclear-group subjects probably had alcoholic cardiomyopathy. The true prevalence of alcoholic cardiomyopathy is higher than the 3% of non-CAD-HF so labeled. Traits influencing development of alcoholic cardiomyopathy may include genetic factors, autoimmune phenomena, and other cardiotoxins.[8]

There Are Unproven and Unknown HF Factors

An underlying genetic substrate probably underlies many cases of idiopathic dilated cardiomyopathy,[20] is likely in alcoholic cardiomyopathy,[21] and indeed may be present in some proportion of HF cases of almost any etiology.[22] Several studies suggest the importance of psychosocial factors, especially depression, in HF risk.[23] Other factors of possible importance in HF include postinfectious or other autoimmune conditions[22] and nutritional factors. If we had been able to ascertain these traits, their addition would have increased the number of factors for many subjects with HF.

This study is limited by the descriptive nature of the data. Assignment of HF factors was based on judgments from chart review only of subjects with HF, precluding case-control comparisons. Use of HF hospitalization as an endpoint leaves unexplored factors in patients with milder HF who are not hospitalized. Incomplete follow-up due to Health Plan termination could affect the data if termination were systematically related to the traits studied. Incomplete chart review of subjects with CAD-HF, due to limited resources, resulted in a small proportion of cases of misdiagnosed HF and of CAD association. We consider it unlikely that any of these limitations affected our main results.

Conclusion

Ready attribution of HF to a single underlying cause often does not fit the facts. In a majority of cases, multiple contributory factors, rather than a specific medical diagnosis, are involved. It is time to retire the traditional disease-specific HF classification. ❖

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Things Done Quickly

Do not be desirous of having things done quickly. Do not look at small advantages. Desire to have things done quickly prevents their being done thoroughly. Looking at small advantages prevents great affairs from being accomplished.

— Confucius, 551-479 BCE, Chinese thinker and social philosopher