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Impact of Chronic Anemia on the New-Onset Atrial Fibrillation in the Elderly: It May Not Be What We Have Thought

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Abstract

Objective

To determine if a clinically significant relation exists between chronic anemia and the new-onset atrial fibrillation (AF) in the elderly population from a community setting.

Patients and Methods

This is a single center community-based retrospective cohort study. Data were collected on 3867 patients over the age of 65 years presenting to the Mercy Medical Center in the year 2006. Patients without AF were divided into anemic and non-anemic groups and were followed over the next two years for the new-onset AF. Chronic anemia was defined as hemoglobin level less than 13g/dl in males and less than 12g/dl in females from two laboratory values checked at least 4 months apart.

Results

Of the 2873 patients without AF, 2382 (83%) patients were non-anemic. 491 patients were anemic. New-onset AF was found in 7.5 % of the anemic patients and 5.5% of the non-anemic patients. After the adjustment for comorbid conditions, chronic anemia is not associated with new-onset AF (p=0.922).

Conclusion

In this study cohort of elderly community-based patients, chronic anemia is not associated with the new-onset AF.

Introduction

Atrial Fibrillation (AF) is the most common arrhythmia in the elderly population. Out of the 2.3 million estimated patients with AF, 1.85 million (80%) are 65 years of age or older.[1] By the year 2050, the number of patients with AF over the age of 65 years is expected to be 4.97 million, which is approximately 88% of the total patients with AF.[1]AF cannot be adequately explained on the basis of current proven risk factors such as age, body mass index, gender, hypertension (HTN) or heart failure (HF) alone. Given the rapidly increasing incidence of AF and the increase in the elderly population, identifying the risk factors for AF and the prevention of AF has become an important clinical and economic priority [National Institutes of Health].[2] The prevalence of anemia in persons aged 65 years and older is 11% in men and 10.2% in women and with age over 85 years, 25% of men and 20% of women develop anemia. [3, 4] Clinical studies completed in the past decade suggest that there is a

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complex relationship among AF, HF, chronic kidney disease (CKD), and anemia. HF is a risk factor for AF [5] and patients with AF and HF, irrespective of which condition develops first, have a poor prognosis. [6] One study reported that anemia is associated with the new-onset HF in the elderly population,[7] and anemia is an independent predictor of death and hospitalizations in elderly patients with HF, coronary artery disease (CAD), or AF. [8, 9]

Therefore, our primary hypothesis is that chronic anemia is a direct determinant of new-onset AF in the elderly community-based population. We propose to address this question by examining the association between chronic anemia and prevalent and incident AF.

Methods

A retrospective cohort study was undertaken using data collected from the medical records of Mercy Medical Center, Mason City, IA. Mercy Medical Center Institutional Review Board approved the study.

Patient Population

We used the following criteria for this study: subjects aged 65 years of age or older, alive throughout the year 2006, presenting to the Mercy Medical Center and its integrated clinics for their initial and follow up medical care. AF and atrial flutter patients were identified using ICD 9 codes 427.3, 427.31 and 427.32. Abstracted comorbid conditions included HF, CKD, CAD, stroke, diabetes, sleep apnea, obesity, HTN, hyperlipidemia, chronic obstructive pulmonary disease (COPD), malignancy, and cardiac valve disorders. We screened 3867 patients initially. We excluded patients who died in the year 2006 (n=121). We characterized patients as deceased if data on death was recorded in the Medicare database. We were unable to identify either a death date or the evidence for follow up for 16 patients and these individuals were excluded from the analysis. The final cohort included 3730 patients. The number of patients with AF in the year 2006 was 857. We divided patients without AF (n=2873) into anemic (n=491) and non-anemic groups (n=2382). These two groups were followed for 2 years starting from January 1st, 2007 to December 31st, 2008 for new-onset AF. We obtained medical records for all hospitalizations and clinic visits.

Definition of Anemia

Anemia was defined based on the World Health Organization (WHO) criteria, which includes hemoglobin levels in males under 13g/dl and females under 12g/dl. Chronic anemia has no precise definition as far as the duration is concerned. Studies have regarded chronic anemia as persisting between 3 to 6 months. We included only patients who had anemia on two different occasions from labs drawn at least 4 months apart. We excluded patients with transient anemia or acute blood loss anemia. The ICD9 codes 280.x (Iron Deficiency Anemia), 282.x (hereditary hemolytic anemia), 283.x (acquired hemolytic anemia), 284.x (aplastic anemia) and 285.x (Other unspecified anemias), were included. We excluded ICD9 code 285.1 which includes acute post hemorrhagic anemia.

Identification of AF

Cases of incident AF were identified by two methods – 12-lead electrocardiograms (ECG) and hospital discharge diagnoses. We considered AF to be present at the time of admission if the discharge diagnosis ICD code indicated AF or atrial flutter. Previous studies have shown that the use of hospital records for diagnosing AF has an accuracy of 98.6% and 24-hour Holter monitor picked up only 0.1% cases of sustained or intermittent AF not identified by the hospital records.[10, 11] The total number of patients with incident AF was 169. Out of the169 patients, 146 had evidence (of AF) from ECG and hospital records, 20 had only ECG evidence and 3 had only hospital records evidence.

Statistical Analysis

We compared demographic and clinical variables between prevalent AF and no AF patients and anemic and non-anemic groups in the year 2006. Comparisons between these groups were made using Chi Square test for the categorical variables

and two sample t-test for the continuous variables. Associations were considered significant at P values below 0.05. Effect of anemia on the prevalent AF was analyzed after adjusting for clinical variables that were associated with AF. Similarly, analysis between patients with incident AF and no AF and anemic and non-anemic groups was done using Chi Square test for categorical variables and two sample t-test for continuous variables. Odds ratio (OR) for incident AF was obtained from multiple logistic regression model that included factors that showed association with new-onset AF. We have used SAS (Statistical Analysis Systems) version 9.2 for analysis of the data.

Results

Baseline Characteristics

The baseline characteristics of the population in the year 2006 (Table 1) show that the mean age of the AF patients (79.6 years) was higher than the patients without AF (77.7 years). The mean age of anemic patients (80.2 years) was higher than that of the non-anemic (77.6 years) patients. The prevalence of anemia in those with AF was 23.8% (204 out of 857) compared to 17.0% (491 out of 2873) in those without AF. The converse, prevalence of AF in those with anemia was 29.3% (204 out of 695) compared to 21.5% (653 out of 3035) in the non-anemic group. Compared to the non-anemic patients, anemic patients had greater burden of AF, CAD, diabetes, HF and CKD. The prevalent AF group (n=857) when compared to those without AF, were older, had greater burden of HF, sleep apnea, CKD, CAD, COPD and valve disorders. Among the variables assessed HF, CAD, sleep apnea, HTN and valve disorders are significantly associated with prevalent AF (Table 2 and 3). Multiple logistic regression analysis, (Table 3) after adjusting for potential confounders, reveals that chronic anemia is not associated with prevalent AF (adjusted OR of 1.13, 95% CI=0.92 to 1.39; P=0.224).

Effect of Anemia on Incident AF:

During the two year retrospective follow-up, the incidence of new-onset AF was 37 (7.5%, P=0.873)

Table 1: Characteristics of the Patient Population in the Year 2006

Two-sample t-test was used for age. Pearson's Chi-Square was used for all other variables.

Variables	AF (n=857)	No AF(n=2873)	P value	Anemia (n=695)	No Anemia (n=3035)	P value
AF				204 (29.35%)	653(21.52%)	< 0.0001
Anemia	204(23.80%)	491(17.09%)	< 0.0001			
Age (mean±SD)	79.62 ± 7.64	77.70 ± 7.83	< 0.0001	80.26 ± 8.00	77.66 ± 7.70	0.0001
Gender (female)	420 (49.01%)	1619 (56.35%)	0.0002	428 (61.58%)	1611 (53.08%)	< 0.0001
Race (white)	851 (99.30%)	2853 (99.30%)	0.7491	689 (99.14%)	3015 (99.34%)	< 0.0001
HF	360 (42.01%)	424 (14.76%)	< 0.0001	248 (35.68%)	536 (17.66%)	< 0.0001
CAD	467 (54.49%)	1035 (36.03%)	< 0.0001	314 (45.18%)	1188 (39.14%)	< 0.0034
CKD	134 (15.64%)	272 (9.47%)	< 0.0001	164 (23.60%)	242 (7.97%)	< 0.0001
Diabetes	256 (29.87%)	714 (24.85%)	0.0033	231 (33.24%)	739 (24.35%)	< 0.0001
Obesity	63 (7. 35%)	155 (5.40)	0.0322	49 (7.05%)	169 (5.57%)	< 0.0322
COPD	190 (22.17%)	444 (15.45%)	0.0001	168 (24.17%)	466 (15.35%)	< 0.0001
Sleep Apnea	72 (8.40%)	88 (3.06%)	0.0001	34 (4.89%)	126 (4.15%)	0.3848
HTN	565 (65.93%)	1755 (61.09%)	0.0103	416 (59.86%)	1904 (62.86%)	0.0103
Hyperlipidemia	364 (42.47%)	1020 (35.50%)	0.0002	250 (35.97%)	1134 (37.36%)	0.0002
CVA	62 (7.23%)	186 (6.47%)	0.4329	48 (6.91%)	200 (6.59%)	0.7624
Cancer	140 (25.09%)	551 (19.18%)	0.0601	158 (22.73%)	533 (17.56%)	0.0015
Valve Disorders	215 (25.09%)	244 (8.49%)	< 0.0001	117 (16.83%)	342 (11.27%)	0.0015
Thyroxine (%)	18.0	12.8	0.39			

AF=Atrial Fibrillation, HF=heart failure, CAD=coronary heart disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, HTN=hypertension, CVA=stroke

Table 2: Demographic and Clinical Variables Associated with AF

Odds Ratio (OR) for AF was obtained from multi-factor logistic regression model that included factors showed an association with AF by either stepwise or backward selection.

Variables	Odds Ratio	Confidence Intervals	P value
Age (per 5 years)	1.131	1.072-1.194	< 0.0001
Sex (M versus F)	1.31	1.106-1.551	0.0018
HF	2.999	2.493-3.608	< 0.0001
CAD	1.362	1.144-1.620	0.0005
Sleep Apnea	2.192	1.546-3.107	< 0.0001
HTN	1.250	1.051-1.486	0.0114
Cancer	0.831	0.668-1.033	0.0956
Valve Disorders	2.434	1.956-3.029	< 0.0001

HF=heart failure, CAD=coronary heart disease, HTN=hypertension.

Table 3: Effect of Anemia on AF after Adjusting for Demographic and Clinical Variables

Variables	Odds Ratio	95% Confidence Limits	P Value
Anemia	1.136	0.926-1.393	0.2214
Age (per 5 years)	1.128	1.069-1.191	<0.0001
Sex (M/F)	1.319	1.113-1.563	0.0014
HF	2.947	2.445-3.553	<0.0001
CAD	1.357	1.141-1.615	0.0006
Sleep Apnea	2.188	1.543-3.103	<0.0001
HTN	1.254	1.055-1.490	0.0104
Cancer	0.823	0.662-1.024	0.0813
Valve Disorder	2.427	1.950-3.021	0.0001

HF=heart failure, CAD=coronary heart disease, HTN=hypertension.

Table 4: Analysis of Incidence of new-onset AF in 2007-2008 from the 2006 patients that did not have AF Comparison of the demographic and clinical variables between those that had anemia and no anemia and between those that had AF in 2007-2008 vs. No AF. Two-sample t-test was used for age. Pearson's Chi-Square was used for all other variables.

Variables	AF (n=169)	No AF(n=2704)	P value	Anemia (n=491)	No Anemia (n=2382)	P value
New-onset AF				37 (7.54%)	132 (5.54%)	0.0873
Age (Mean ± SD)	80.33 ± 7.39	77.63 ± 7.84	<.0001	80.09 + 8.13	77.31 + 7.70	<0.0001
Gender (female)	70 (41.42%)	1549(57.29%)	<.0001	173 (35.23%)	1081(45.38%)	<0.0001
Race (white)	169 (100%)	2684(99.26%)	0.9391	487 (99.19%)	2366(99.33%)	0.0575
HF	54 (31.95%)	370 (13.68%)	<.0001	122 (24.85%)	302 (12.68%)	<0.0001
CAD	85 (50.30%)	950 (35.13%)	<0.0001	186 (37.88%)	849 (35.64%)	0.3466
CKD	35 (20.71%)	237 (8.76%)	<0.0001	99 (20.16%)	173 (7.26%)	<0.0001
Diabetes	50 (29.59%)	664 (24.56%)	0.1422	160 (32.59%)	554 (23.26%)	<0.0001
Obesity	7 (4.14%)	148 (5.47%)	0.4573	29 (5.91%)	126 (5.29%)	0.5818
COPD	50 (29.59%)	394 (14.57%)	<0.0001	103 (20.98%)	341 (14.32%)	0.0002
Sleep Apnea	10 (5.92%)	78 (2.88%)	0.0264	15 (3.05%)	73 (3.06%)	0.9910
HTN	119 (70.41%)	1636 (60.50%)	0.0104	296 (60.29%)	1459 (61.25%	0.6894
Hyperlipidemia	70 (41.42%)	950 (35.13%)	0.0975	161 (32.79%)	859 (36.06%)	0.1677
CVA	11 (6.51%)	175 (6.47%)	0.9849	25 (5.09%)	161 (6.76%)	0.1716
Cancer	30 (17.75%)	521 (19.27%)	0.6272	120 (24.44%)	431 (18.09%)	0.0011
Valve Disorder	27 (15.98%)	217 (8.03%)	0.0003	59 (12.02%)	185 (7.77%)	0.0021

AF=Atrial Fibrillation, HF=heart failure, CAD=coronary heart disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, HTN=hypertension, CVA=stroke

Table 5: Demographic and clinical variables associated with new-onset AF. Odds Ratio (OR) for AF was obtained from multi-factor logistic regression model that included factors that showed an association with AF by either stepwise or backward selection.

Variables	Odds Ratio	95% Confidence Limits	P Value
Age (per 5 years)	1.243	1.119-1.382	<0.0001
Sex (M vs F)	1.850	1.326-2.581	0.0003
HF	1.777	1.200-2.632	0.0041
CKD	2.005	1.260-3.190	0.0033
COPD	1.971	1.354-2.870	0.0004
HTN	1.953	1.353-2.818	0.0003
Valve Disorder	1.522	0.959-2.415	0.0747
Cancer	0.823	0.662-1.024	0.0813
Valve Disorder	2.427	1.950-3.021	0.0001

HF=heart failure, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, HTN=hypertension.

Table 6: Effect of Anemia on incidence of AF after adjusting for demographic and clinical variables.

Variables	Odds Ratio	95% Confidence Limits	P Value
Anemia	1.020	0.683-1.524	0.9222
Age (per 5 years)	1.243	1.117-1.382	<0.0001
Sex (M/F)	1.853	1.327-2.587	0.0003
HF	1.775	1.198-2.630	0.0042
CKD	1.999	1.252-3.192	0.0037
COPD	1.968	1.350-2.869	0.0004
HTN	1.952	1.353-2.817	0.0004
Valve Disorder	1.520	0.958-2.414	0.0757

HF=heart failure, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, HTN=hypertension.

patients in the anemic group (n=491) compared to 132 (5.5%) in the non-anemic group (n=2382). Patients with new-onset AF when compared to those without AF were older, more frequently males, had greater burden of CKD, CAD, COPD, diabetes, HTN, and valve disorders. Since AF could occur as a result of the preceding conditions like HF, we evaluated the anemia-AF relationship after adjusting for CHF, CKD, HTN, COPD and valve disorders. After multivariable analysis with adjustment for potential confounders, anemia was not associated with incident AF (adjusted OR of 1.02 95% CI =0.68 to 1.52; P=0.922, see Table 6). After adjustment of variables with multiple logistic regression analysis, CKD, COPD, HTN, and HF were significantly associated with the new-onset AF (Tables 5 and 6). Interestingly, CAD and sleep apnea though significantly associated with prevalent AF, did not predict the incident AF. Despite high prevalence of CAD in the new-onset AF patients (50.3%), CAD did not predict new-onset AF.

Discussion

The primary analysis of this study demonstrates that chronic anemia alone is not a determinant for new-onset AF in an elderly community-based population. To our knowledge, there are no previous studies on anemia and incident AF in an elderly cohort. This comprehensive study in a large community-based elderly population shows that chronic anemia alone is not directly associated with incident and prevalent AF. Our study analysis shows that elderly patients with chronic anemia but without underlying comorbid disease are not prone to incident AF. Rather, chronic anemia seems to require other comorbid factor(s) like HF to precipitate AF as suggested in this study cohort. The study is unique as it is the first to show that chronic anemia is not directly associated with AF which has significant implications for this rapidly growing segment of the population. The study findings also question whether in elderly individuals, the mechanism of chronic

anemia in AF is different from that of acute anemia. Dynamics such as baseline cardiac status, severity of anemia and rapidity of onset of anemia can affect heart rate, hemodynamic status and symptoms. Acute severe anemia can cause hemodynamic stress on the heart due to the sudden drop in hemoglobin. Rapid onset of anemia can cause tachycardia as compensatory physiologic responses have less time to adapt. The observation that acute severe anemia can cause new- onset AF was first reported by Buxbaum et al.[12] Heart rate has also been shown to increase linearly in response to acute isovolemic anemia in healthy adults.[13]

In case of chronic anemia, gradual decrease in hemoglobin levels could allow the heart to adapt to a certain extent, before HF or AF occurs. One echocardiographic study reported that chronic severe anemia is well tolerated by the aging heart, in the absence of overt heart disease.[14] The study included 41 elderly patients over the age of 65 years
with recently established chronic anemia (3-5 months) and no history of heart disease, COPD or CKD.

Certain age-related factors in the elderly could assist in adapting to gradual decrease in hemoglobin levels before a certain threshold is reached. There is diminished intrinsic inotropic response of the myocardium to catecholamines and age related decrease in chronotropic response to sympathetic stimulation.[15, 16] Decreased muscle mass with age and subsequent decreased need for blood supply and oxygen can help elderly adapt to the gradual decrease in hemoglobin levels.[17, 18] The degree of physical activity is also less in the elderly. It is likely that majority of elderly patients in our study with chronic anemia had adequate levels of hemoglobin to lower their risk for HF and new-onset AF.
In contrast to a direct association of anemia with incident AF, our analysis suggests that HF, COPD, HTN, CKD and valve disorders are strongly associated with incident AF. Framingham study data showed HF to be the strongest risk factor for AF.[5] While chronic anemia is associated with incident HF in the elderly, [7] it is plausible for elderly patients with chronic anemia left untreated for a prolonged period to develop congestive HF and subsequent AF. The most common disease listed as primary diagnosis for patients hospitalized with AF was HF.[19] Like AF, HF is an epidemic in the elderly and its incidence approaches 10 per 1000 population after 65 years of age.[20] Data suggest that adjustment for comorbid disease largely neutralizes the effect of anemia on physical function; however, persistent anemia results in poor survival of HF patients. [21]
It is unclear how long anemia must be present and what hemoglobin threshold is required (if any) before elderly patients are at increased risk for HF and AF. There is a clear dose-response relationship between severity of anemia and risk of death.[21] The subgroup of patients with HF and anemia are likely to be at higher risk for incident AF compared to those anemic patients without HF.

Limitations

Our study is retrospective in design and, therefore, subject to the inherent limitations of such a design. The large cohort, however, gives excellent power and even though we employed strict parameters for diagnosing new-onset AF, asymptomatic cases of paroxysmal AF could have been missed. Also, the incidence of AF could be underestimated due to the short follow-up period of 2 years. The contribution of hemodilutional anemia could not be estimated but we tried to achieve consistency by including only chronic anemia patients. Despite strict inclusion criteria, it is still possible that we could have underestimated the number of anemia patients as anemia is often under-diagnosed in the elderly.[28] Our findings are confined by design to the community-based elderly population and, therefore, cannot be generalized to all age groups.

Conclusions

The results of our study support the conclusion that chronic anemia alone is not a determinant of new-onset AF in a large elderly non-clinical trial community-based population. In elderly patients without underlying comorbid factors, intervening to correct anemia might not be efficacious or necessary in preventing AF. However, our data show that HF, COPD, CKD, and HTN are risk factors for the new-onset AF in this population. Chronic anemia may, therefore, indirectly impact

AF by multiple, interrelated mechanisms. One likely mechanism is through HF. Studies are needed to assess the hemoglobin threshold and the time period after which elderly chronic anemic patients are most likely to develop HF and subsequent AF. This information would enable clinicians to identify the elderly subgroups who might benefit from treatment for chronic anemia.

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