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Epstein Barr Virus and Atrial Fibrillation - A Causal Link?

Ilija Barukčić[1]

[1] Internist, Horandstrasse, DE-26441 Jever, Germany

Correspondence: Ilija Barukčić, Horandstrasse, DE-26441 Jever, Germany. Tel: 0049-(0)4466-333.

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Abstract

Objective: Atrial fibrillation (AF) is very frequent and clinically significant arrhythmia. The incidence of atrial fibrillation is continuously rising. Meanwhile several risk factors for AF development have been identified but the etiology is not cleared.

Methods: A systematic review and re-analysis of studies which investigated the relationship between AF and some risk factors was conducted. The method of the conditio sine qua non relationship, the method of the conditio per quam relationship, the method of the exclusion relationship and the mathematical formula of the causal relationship k were used to proof the hypothesis. Significance was indicated by a p-value of less than 0.05.

Results: The studies analyzed were able to provide direct and indirect evidence that AF is caused by a process of inflammation while a direct identification of the factor causing AF was not possible. Still, it appears to be very probable that Epstein-Barr virus (EBV) is the cause of AF.

Conclusion: Atrial fibrillation (AF) appears to be caused by an EBV inflammatory process.

Keywords: Epstein-Barr virus, atrial fibrillation, causal relationship

1. Introduction

In general, atrial fibrillation (AF) is regarded as a disease of the elderly, with a substantially increase (Chugh et al., 2014) of incidence and prevalence with age but asymptomatic atrial fibrillation (AF) has been detected by implanted cardiac devices (Glotzer & Ziegler, 2013) too which is generally undetected in the clinical setting. Thus far, more than 10% of the general population older than 80 years suffer from AF. Nonetheless, about 90 % of the elderly patients have none AF. Among other measures, long-term use of oral anticoagulants (OACs) for stroke prevention for people aged over 75 who have atrial fibrillation is required (Mant et al., 2007). To date, the precise mechanisms involved in AF is not well understood. In particular, people who are living healthy lives and have no other medical problems develop sometimes atrial fibrillation too. In addition to cardiac causes such as congestive heart failure or valve disease other common risk factors (Wasmer et al., 2017) of atrial fibrillation like cigarette smoking, diabetes mellitus, hypertension (Kirchhof et al., 2012), prevalent coronary artery disease (Benjamin et al., 1994) chronic kidney disease (Psaty et al., 1997) have been identified and are regarded as well-established risk factors of AF. Less well-established risk factors are alcohol consumption, genetic factors (Fox et al., 2004), left atrial (LA) enlargement (Psaty et al, 1997) and other. The diagnosis of AF is secured by an cost-effective electrocardiogram (ECG) showing the typical pattern of absolutely irregular RR intervals and no discernible, distinct P waves while both symptomatic and asymptomatic episodes of AF (Kirchhof et al., 2009; Savelieva & Camm, 2000) must be distinguished. In general, ECG monitoring is of further help for the management of AF. Several studies hypothesized even that inflammation (Aviles et al., 2003; Issac et al., 2007; Kirchhof et al., 2013) is involved in the pathogenesis and development of AF (Stroke Risk in Atrial Fibrillation Working Group, 2007; Cha et al., 2018).

2. Material and Methods

2.1 Material

2.1.1 Search Strategy

To answer the questions addressed in this paper, the electronic database PubMed was searched for appropriate studies conducted in any country which investigated the relationship between atrial fibrillation and inflammation. The search in PubMed was performed while using some medical key words atrial fibrillation and virus and glucocorticoid et cetera. The articles found where saved as a *.txt file while using the support of PubMed. The created *.txt file was converted into a *.pdf file. The abstracts where studied within the *.pdf file. Those articles

were considered for a re-view which provided access to data without any data access barrier. Additionally the reference list of identified articles was used as a potential source of articles appropriate for this study.

2.1.2. The 2x2 Table

The meaning of the abbreviations a_t, b_t, c_t, d_t, N_t of the data table used are explained by a 2 by 2-table Table 1.

Table 1. The sample space of a contingency table.

		Conditioned B_t (Outcome)		
		Yes = +1	**Not = +0**	**Total**
Condition A_t (risk factor)	**Yes =+1**	a_t	b_t	**A_t**
	Not = +0	c_t	d_t	$\underline{A}_t$
	Total	**B_t**	$\underline{B}_t$	***n_t***

It is $(a_t+b_t) = A_t$, $(c_t+d_t) = \underline{A}_t$, $(a_t+c_t) = B$, $(b_t+d_t) = \underline{B}_t$ and $a_t+b_t+c_t+d_t=n_t$. Equally, it is $B_t+\underline{B}_t = A_t + \underline{A}_t = n_t$.

2.1.3 The Studies Used to Analyze the Conventional Risk Factor

The table (Table 2) presents the data of some studies which analyzed the relationship between AF and some risk factors. The contradictions are signed by red color.

Table 2. The relationship between some classical risk factors and AF.

Study Id	Year	Country	Risk Factor	Case_P	Case_T	Con_P	Con_T	k	p-val	X²(SINE)	X²(IMP)	X²(IMP^SINE)	X²(EXCL)
Wang et al.	2015	China	Family history	12	285	11	300	0.01398	0.15872	260.55	4.79	265.34	6.21
Wang et al.	2015	China	Alcohol	97	285	89	300	0.04688	0.03726	123.36	42.11	165.46	82.74
Wang et al.	2015	China	Smoke	147	285	159	300	-0.01422	0.06220	66.34	82.10	148.44	145.44
Chao et al.	2018	Taiwan	Diabetes mellitus	3770	15756	2884	14658	0.0513	3.5E-20	9117.30	1249.56	10366.86	3037.25
Wang et al.	2015	China	Diabetes mellitus	86	285	90	300	0.00191	0.0717	138.25	45.51	183.77	67.19
Wang et al.	2015	China	Dyslipidemia	117	285	112	300	0.03808	0.04422	98.44	54.29	152.73	106.89
Kim et al.	2014	USA	Hyperlipidemia	6439	20852	34561	104260	-0.01801	8.3E-12	9961.64	29132.39	39094.04	2999.10
Kim et al.	2014	USA	Hypertension	5876	20852	26360	104260	0.02468	3.4E-19	10755.11	21554.26	32309.38	2726.45
Chao et al.	2018	Taiwan	Hypertension	11679	15756	9005	14658	0.13594	4.5E-125	1054.70	3919.99	4974.69	15250.08
Wang et al.	2015	China	Hypertension	220	285	221	300	0.04091	0.04701	14.60	110.25	124.85	278.31
Wang et al.	2015	China	Cerebral infarction	91	285	82	300	0.05034	0.03448	131.38	38.39	169.77	76.08
Chao et al.	2018	Taiwan	Previous stroke/TIA	7772	15756	4724	14658	0.17366	2.1E-203	4045.21	1785.49	5830.69	8666.46
Wang et al.	2015	China	Arteriosclerosis	201	285	190	300	0.07636	0.01277	24.46	91.84	116.31	243.87
Chao et al.	2018	Taiwan	Prev. vascular disease	2004	15756	5230	14658	-0.2694	0	12002.02	3780.44	15782.45	809.64
Chao et al.	2018	Taiwan	Congestive heart failure	8680	15756	3042	14658	0.35252	0	3177.37	789.18	3966.55	11207.97
Kim et al.	2014	USA	Cardiovascular disease	1439	20852	5355	104260	0.02902	3.7E-24	18072.37	4220.00	22292.37	403.81

Table 3. The relationship between a therapy with (methyl-) prednisolon and permanent AF

		The Study of Dernellis & Panaretou, 2004 Permanent AF <B>		
		Yes	No	Total
Methylprednisolone 16 mg <A>	Yes	**1**	15	16
	No	51	37	88
	Total	52	52	104
		k =	**- 0.3731**	
		p value (k) =	**0.0001**	
		95% CI (k) =	(0.1538;0.5924)	
		<A> EXCLUDES	<B> and vice versa	
		p(EXCL)=	0.99038462	
		X²(EXCL)=	**0.0204**	

2.1.4 Methylprednisolone and Permanent AF

Dernellis & Panaretou (Dernellis & Panaretou, 2004) investigated whether a low-dose glucocorticoid therapy (16 mg methylprednisolone for 4 weeks tapered to 4 mg for 4 months) compared to placebo is able to reduce AF.

2.2 Methods

2.2.1 Statistical Analysis

All statistical analyses (Barukčć, 1989; Barukčć, 2005; Barukčć, 2006; Barukčć, 2016; Barukčć, 2017; Barukčć, 2018) were performed with Microsoft Excel version 14.0.7166.5000 (32-Bit) Software (Microsoft GmbH. Munich. Germany). The level of significance was set to 0.05. The probabilities of the contingency table are viewed by the following table (Table 4).

Table 4. The probabitlities of a contingency table

		Conditioned B_t		
		Yes = +1	**No = +0**	**Total**
Condition A_t	**Yes =+1**	**$p(a_t) = p(A_t \cap B_t)$**	$p(b_t)$	$p(A_t)$
	No = +0	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
	Total	$p(B_t)$	$p(\underline{B}_t)$	**1**

In this context, it is $p(a_t)=p(A_t \cap B_t)$, $p(A_t) = p(a_t)+p(b_t)$ or $p(A_t)= p(A_t \cap B_t)+ p(b_t) =p(A_t \cap B_t)+p(A_t \cap \underline{B}_t)$ while $p(A_t)$ is not defined as $p(a_t)$. In the same context, it is $p(B_t) = p(a_t)+p(c_t) = p(A_t \cap B_t) +p(c_t)$ and equally in the same respect $p(\underline{B}_t) = 1- p(B_t) =p(b_t)+p(d_t)$. Furthermore, the joint probability of A_t and B_t is denoted in general by $p(A_t \cap B_t)$. Thus far, it is $p(A_t \cap B_t) = p(A_t) - p(b_t) = p(B_t) - p(c_t)$ or in other words it follows clearly that $p(B_t) + p(b_t) - p(c_t) = p(A_t)$. Thus far, define $\Lambda = p(b_t) - p(c_t)$, under conditions of probability theory and we obtain $p(B_t) + \Lambda = p(A_t)$. In general, it is $p(a_t)+p(c_t)+p(b_t)+p(d_t) = 1$.

2.2.2 Independence

In the case of independence of A_t and B_t (Kolmogoroff, 1933) it is generally valid that

$$p\left(A_t \cap B_t\right) \equiv p\left(A_t\right) \times p\left(B_t\right) \tag{1}$$

2.2.3 Exclusion (A_t Excludes B_t and Vice Versa Relationship)

The mathematical formula of the *exclusion* relationship (A_t excludes B_t and vice versa) of a population was defined (Barukčć, 1989; Barukčć, 2005; Barukčć, 2006; Barukčć, 2016; Barukčć, 2017; Barukčć, 2018) as

$$p\left(A_t \mid B_t\right) \equiv \frac{b_t + c_t + d_t}{N_t} \equiv 1 - p\left(a_t\right) \equiv p\left(b_t\right) + p\left(c_t\right) + p\left(d_t\right) \equiv p\left(c_t\right) + \left(1 - p\left(B_t\right)\right) \equiv p\left(b_t\right) + \left(1 - p\left(A_t\right)\right) \equiv +1 \tag{2}$$

and used to proof the hypothesis: A_t *excludes* B_t and vice versa.

2.2.4 Necessary Condition (Conditio Sine Qua Non)

The mathematical formula of the *necessary* condition relationship (*conditio sine qua non*) of a population was defined (Barukčć, 1989; Barukčć, 2005; Barukčć, 2006; Barukčć, 2016; Barukčć, 2017; Barukčć, 2018) as

$$p\left(A_t \leftarrow B_t\right) \equiv \frac{a_t + b_t + d_t}{N_t} \equiv p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right) \equiv p\left(a_t\right) + \left(1 - p\left(B_t\right)\right) \equiv +1 \tag{3}$$

and used to proof the hypothesis: *without* A_t *no* B_t .

2.2.5. Sufficient Condition (Conditio per Quam)

The mathematical formula of the *sufficient* condition relationship (conditio per quam) of a population was defined (Barukčć, 1989; Barukčć, 2005; Barukčć, 2006; Barukčć, 2016; Barukčć, 2017; Barukčć, 2018) as

$$p\left(A_t \rightarrow B_t\right) \equiv \frac{a_t + c_t + d_t}{N_t} \equiv p\left(a_t\right) + p\left(c_t\right) + p\left(d_t\right) \equiv p\left(d_t\right) + p\left(B_t\right) \equiv +1 \tag{4}$$

and used to proof the hypothesis: *if* A_t *then* B_t .

2.2.6 The X^2 Goodness of Fit Test of a Necessary Condition

Under conditions where the chi-square goodness of fit test (Pearson, 1900) cannot be used it is possible to use an approximate and conservative (one sided) confidence interval known as *the rule of three* (Rumke, 1975; Hanley et al., 1983; Louis, 1981; Jovanovic et al., 1997). Using *the continuity correction (Yates, 1934),* the chi-square value of a conditio sine qua non distribution is derived as

$$\chi^2\left(\mathrm{SINE}\right) \equiv \frac{\left(c_t - \left(\frac{1}{2}\right)\right)^2}{\left(B_t\right)} + 0 = 0 \tag{5}$$

2.2.7 The X^2 Goodness of Fit Test of the Exclusion Relationship

The chi square value with degree of freedom 2-1=1of the exclusion relationship (Barukčć, 1989; Barukčć, 2005; Barukčć, 2006; Barukčć, 2016; Barukčć, 2017; Barukčć, 2018) with a *continuity correction* (Yates, 1934) can be calculated as

$$X^2\left(EXCL\right) = \frac{\left(-a_t\right)^2}{A_t} \tag{6}$$

2.2.8 The Mathematical Formula of the Causal Relationship k

The mathematical formula of the causal relationship k (Barukčć, 1989; Barukčć, 2005; Barukčć, 2006; Barukčć, 2016; Barukčć, 2017; Barukčć, 2018) is defined *at every single event, at every single Bernoulli trial t,* as

$$k\left(A_t, B_t\right) \equiv \frac{\left(p\left(A_t \cap B_t\right) - \left(p\left(A_t\right) \times p\left(B_t\right)\right)\right)}{\sqrt[2]{\left(p\left(A_t\right) \times p\left(\underline{A}_t\right)\right) \times \left(p\left(B_t\right) \times p\left(\underline{B}_t\right)\right)}} \tag{7}$$

where A_t denotes the cause and B_t denotes the effect. The chi-square distribution can be applied to determine the significance of causal relationship k. Pearson's concept of correlation (Pearson, 1896) is not identical with causation, causation is not identical with correlation. In particular, the relationship between correlation and causation has already been discussed in many publications (Barukčć, 1989; Barukčć, 2005; Barukčć, 2006; Barukčć, 2016; Barukčć, 2017; Barukčć, 2018). Thus far, repeating itself over and over again on this topic is only a waste of time and will not contribute anything new to further scientific progress.

2.2.9 The 95% Confidence Interval of the Causal Relationship k

A confidence interval (CI) of the causal relationship k calculated from the statistics of the observed data can help to estimate the true value of an unknown population parameter with a certain probability. Let the sample mean S be

$$S = \overline{k\left(A_t, B_t\right)} = \frac{k\left(A_1, B_1\right) + k\left(A_2, B_2\right) + \ldots + k\left(A_n, B_n\right)}{n} = \frac{\sum_{t=+1}^{n} k\left(A_t, B_t\right)}{n} \tag{8}$$

Since $k(A_t,B_t)$ is Bernoulli(p) distributed with $E(k(A_t,B_t)) = (1\times p(k(A_t,B_t))) + (0\times(1- p(k(A_t,B_t))) = p(k(A_t,B_t))$ where $E(k(A_t,B_t))$ denotes the expected value of $k(A_t,B_t)$ it is

$$E\left(S\right) = p\left(k\left(A_t, B_t\right)\right) \text{ and } \sigma\left(S\right)^2 = \frac{p\left(k\left(A_t, B_t\right)\right) \times \left(1 - p\left(k\left(A_t, B_t\right)\right)\right)}{n} \tag{9}$$

where $\sigma(S)^2$ denotes the variance of the sampling distribution of $p(k(A_t,B_t))$. When the sample size is not too small, the central limit theorem based normal approximation can be used to estimate the confidence interval (CI) as

$$p\left(k\left(A_t, B_t\right)\right) \pm \left(Z \times \sqrt[2]{\frac{p\left(k\left(A_t, B_t\right)\right) \times \left(1 - p\left(k\left(A_t, B_t\right)\right)\right)}{n}}\right) = p\left(k\left(A_t, B_t\right)\right) \pm \left(\sqrt[2]{\frac{Z^2}{n} \times p\left(k\left(A_t, B_t\right)\right) \times \left(1 - p\left(k\left(A_t, B_t\right)\right)\right)}\right) \tag{10}$$

where $p(k(A_t,B_t))$ denotes the proportion of successes in a Bernoulli trial process and Z is the $(1–(\alpha/2))$ quantile of a standard normal distribution. For a 95% confidence level Z ~ 1.96. For an unknown standard deviation the Student's t distribution t can be used as the critical value. Still, it is known that $\sigma(S)^2$ has the maximum value $(1/(4\times n))$ when p=1/2 and approximately we obtain

$$p\left(k\left(A_t,B_t\right)\right) \pm\left(\sqrt[2]{\frac{Z?}{4\times n}}\right) \Leftrightarrow p\left(k\left(A_t,B_t\right)\right) \pm\left(\sqrt[2]{\frac{.96^2}{4\times n}}\right) \approx p\left(k\left(A_t,B_t\right)\right) \pm\left(\sqrt[2]{\frac{1}{n}}\right) \tag{11}$$

The proposed approximation is of use even under circumstances where p(…) = 0.9999 … 999 ~ p=1. In this context, we obtain the critical value $p_{critical}$ approximately as $p_{critical} = 1 – (1/(n))^{1/2}$. In particular, the concept of Chebyshev's inequality is profound because the same inequality is true for every distribution even if the distribution isn't normal. Thus far, Chebyshev's inequality allows calculating the 95% confidence of the causal relationship k and so by the Chebyshev inequality it is

$$p\left\{p\left(k\left(A_t,B_t\right)\right)-c\times\sqrt[2]{\sigma\left(S\right)^2}<S<p\left(k\left(A_t,B_t\right)\right)+c\times\sqrt[2]{\sigma\left(S\right)^2}\right\}\geq 1-\frac{1}{c^2} \tag{12}$$

were the right side has the value 0.95 when $c =(20)^{1/2}$. This is the case since $(1-(1/c^2))=0.95$ or $0.05 = (1/c^2)$ or $c^2= (1/0.05)$ or $c^2 = (100/5)$ or $c^2 = 20$ or $c =(20)^{1/2}$. Thus far, if S does lie in the interval

$$\left\{p\left(k\left(A_t,B_t\right)\right)-\sqrt[2]{20\times\sigma\left(S\right)^2},p\left(k\left(A_t,B_t\right)\right)+\sqrt[2]{20\times\sigma\left(S\right)^2}\right\} \tag{13}$$

then $p(k(A_t,B_t))$ itself must be in the interval

$$\left\{S-\sqrt[2]{20\times\sigma\left(S\right)^2},S+\sqrt[2]{20\times\sigma\left(S\right)^2}\right\} \tag{14}$$

which is equally the 95% confidence interval for an unknown parameter $p(k(A_t,B_t))$. Again, $\sigma(S)^2$ has the maximum value $(1/(4\times n))$ when p=1/2, so we have

$$\left\{S-\sqrt[2]{\frac{20\times1}{4\times n}},S+\sqrt[2]{\frac{20\times1}{4\times n}}\right\} \tag{15}$$

or **the 95% interval for the causal relationship k** as

$$\left\{k\left(A_t,B_t\right)-\sqrt[2]{\frac{5}{n}},k\left(A_t,B_t\right)+\sqrt[2]{\frac{5}{n}}\right\} \tag{16}$$

2.2.10 Hypergeometric distribution

The probability of having exactly a_t (Table 1) successes or the significance of the causal relationship k can be tested under conditions of sampling without replacement by the hypergeometric distribution as

$$p\left(a_t\right)=\frac{\binom{A_t}{a_t}\times\binom{N_t-A_t}{B_t-a_t}}{\binom{N_t}{B_t}} \tag{17}$$

2.2.11 Odds Ratio

The odds ratio (OR) is given (Barukčć, 2018) by

$$OR\left(A_t,B_t\right)\equiv\frac{a_t/b_t}{c_t/d_t}=\frac{a_t\times d_t}{c_t\times b_t} \tag{18}$$

Under conditions were c_t=0 there is a conditio sine qua non relationship while the odds ratio collapses. Under conditions were b_t=0 we have a conditio per quam relationship but the odds ratio collapses again, since to date it is not generally accepted (Barukčić & Barukčić, 2016b; Barukčić, 2018d) to divide by zero. To avoid confusion on this issue, 0.5 is added to the cells a_t, b_t, c_t, d_t (Barukčć, 2018), if zero causes some problems with the calculation of the odds ratio or its standard error which is often very misleading. In point of fact, the odds ratio (OR) is nothing more but *Yule's coefficient of association Q* (Barukčć, 2018) re-written (Barukčć, 2018) in a non-normalized form and given by

$$Q\left(A_t,B_t\right)\equiv\frac{OR\left(A_t,B_t\right)-1}{OR\left(A_t,B_t\right)+1}=\frac{\frac{\left(a_t\times d_t\right)}{\left(b_t\times c_t\right)}-1}{\frac{\left(a_t\times d_t\right)}{\left(b_t\times c_t\right)}+1}=\frac{\frac{\left(a_t\times d_t\right)-\left(b_t\times c_t\right)}{\left(b_t\times c_t\right)}}{\frac{\left(a_t\times d_t\right)+\left(b_t\times c_t\right)}{\left(b_t\times c_t\right)}}=\frac{\left(a_t\times d_t\right)-\left(b_t\times c_t\right)}{\left(a_t\times d_t\right)-\left(b_t\times c_t\right)} \tag{19}$$

If Q = 0 then there is no association. Yule's coefficient of association, Q, and thus far Odds ratio itself, has been severely criticized by Karl Pearson (1857–1925), the long-time and rarely challenged leader of statistical science and by Heron (Barukčć, 2018). The standard error and 95% confidence interval of the odds ratio (OR) can be calculated according to Altman (Altman, 1991). The standard error of the log odds ratio is given by

$$SE\left(\ln\left(OR\left(A_t,B_t\right)\right)\right)\equiv\sqrt[1]{\frac{1}{a_t}+\frac{1}{b_t}+\frac{1}{c_t}+\frac{1}{d_t}} \tag{20}$$

where ***ln*** denotes the logarithmus naturalis. The 95% confidence interval of the odds ratio is given by

$$95\%\,CI=\exp\left(\ln\left(OR\left(A_t,B_t\right)\right)-\left(1.96\times SE\left(\ln\left(OR\left(A_t,B_t\right)\right)\right)\right)\right)\ \text{to}\ \exp\left(\ln\left(OR\left(A_t,B_t\right)\right)+\left(1.96\times SE\left(\ln\left(OR\left(A_t,B_t\right)\right)\right)\right)\right) \tag{21}$$

2.2.12 The unknown population proportion π_{upper}

Tests of hypotheses concerning the sampling distribution of the sample proportion **p** (i. e. conditio sine qua non p(SINE), conditio per quam p(IMP) et cetera) can be performed using the normal approximation. The calculation of the rejection region based on the sample proportion to construct a confidence interval for an unknown population proportion π_{upper} can be performed under conditions of *sampling without replacement* by the formula

$$\pi_{\text{critical upper}}=\left(p-\frac{1}{2\times n}\right)-\left(Z\times\sqrt[2]{\left(\frac{p\times(1-p)}{n}\right)\times\left(\frac{N-n}{N-1}\right)}\right) \tag{22}$$

while the term ((N-n)/(N-1)) denotes *the finite population correction* (Isserlis, 1918).

2.2.13 The Chi Square Distribution

The following critical values of the chi square distribution as visualized by Table 5 are used in this publication.

Table 5. The critical values of the chi square distribution (degrees of freedom: 1)

	p-Value	One sided X^2	Two sided X^2
	0.1000000000	1.642374415	2.705543454
	0.0500000000	**2.705543454**	**3.841458821**
	0.0400000000	3.06490172	4.217884588
	0.0300000000	3.537384596	4.709292247
	0.0200000000	4.217884588	5.411894431
	0.0100000000	5.411894431	6.634896601
The chi square distribution	0.0010000000	9.549535706	10.82756617
	0.0001000000	13.83108362	15.13670523
	0.0000100000	18.18929348	19.51142096
	0.0000010000	22.59504266	23.92812698
	0.0000001000	27.03311129	28.37398736
	0.0000000100	31.49455797	32.84125335
	0.0000000010	35.97368894	37.32489311
	0.0000000001	40.46665791	41.82145620

3. Results

3.1 Classical Risk Factors (CRF) and Atrial Fibrillation (AF)

Some of the studies analysed provided additional data about the relationship between *classical risk factors* like family history of AF, alcohol, smoking, diabetes mellitus, hyperlipidemia, hypertension, previous stroke/TIA, arteriosclerosis, congestive heart failure, cardiovascular disease and atrial fibrillation with conflicting results on its role as an etiological factor. The data are viewed by Table 2. The hypothesis *without* CRF *no* AF was tested. The hypothesis *if* CRF *then* AF was testet too. In fact, the null-hypothesis alltogether had to be rejected.

Proof.

H_0: Without *family history of AF* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If family history of AF then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: Without *alcohol* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If alcohol then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: Without *smoking* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If smoking then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: Without *diabetes mellitus* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If diabetes mellitus then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: Without *dyslipidemia* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If hyperlipidemia then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: Without *hypertension* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If hypertension then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: Without *cerbral infarction* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If previous stroke/TIA then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: Without *arteriosclerosis* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If previous vascular disease then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: Without *cong. heart failure* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If congestive heart failure then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: Without *cardiovasc. disease* no atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

H_0: If cardiovascular disease then atrial fibrillation. (Null hypothesis rejected, no significant result (Table 2)).

Neither family history of AF nor alcohol nor smoking nor diabetes mellitus nor hyperlipidemia nor hypertension nor previous stroke/TIA nor arteriosclerosis nor congestive heart failure nor cardiovascular disease et cetera can be regarded as a cause or as the cause of AF. **Q. e. d.**

3.1 A therapy with (Methyl) Prednisolone and Atrial Fibrillation(AF)

Little or none direct information is available on the effect of an anti-viral or anti-inflammatory therapy on the reduction of atrial fibrillation. According to Engelmann and Svendsen (Engelmann & Svendsen, 2005) a treatment with glucocorticoids seems to reduce AF. The systematic review and meta-analysis of observational studies of Liu et al. (Liu et al., 2007) suggests that increased CRP levels are related to greater risk of AF recurrence. Henningsen et al. (Henningsen et al., 2009) investigated the role of inflammatory processes in the development of atrial fibrillation and were able to provide some evidence that patients with AF had elevated levels of inflammatory markers. In general, a low-dose glucocorticoid therapy (i. e. 16 mg methylprednisolone for 4 weeks tapered to 4 mg for 4 months) compared to placebo should have no effect on (recurrent or permanent) AF. In other words we do expect that a therapy with (methyl-) *prednisolone and AF are independent* of each other. Dernellis & Panaretou (Dernellis & Panaretou, 2004) investigated the effect of a low-dose glucocorticoid therapy (16 mg methylprednisolone for 4 weeks tapered to 4 mg for 4 months) compared to placebo on AF. According to Dernellis & Panaretou (Dernellis & Panaretou, 2004) a therapy with (methyl-) prednisolone was able to reduce recurrent AF from 50% in the placebo group to 9.6% in the glucocorticoid group. Furthermore, permanent AF was reduced by a therapy with (methyl-) prednisolone from 29% in the placebo group to 2% in the glucocorticoid group. The results were significant. The data of the study of Dernellis & Panaretou (Dernellis & Panaretou, 2004) were reanalysed (Table 3).

Null Hypothesis:

A therapy with (methyl-) prednisolon does not prevent from permanent AF. In other words, $k = 0$.

Alternative Hypothesis:

A therapy with (methyl-) prednisolon does prevent from permanent AF. In other words, $k < 0$.

The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0.05.

Proof.

The results of the re-analyses of the data of the study of Dernellis & Panaretou (Dernellis & Panaretou, 2004) which investigated the relationship between a low-dose glucocorticoid therapy (i. e. 16 mg methylprednisolone for 4 weeks tapered to 4 mg for 4 months) compared to placebo and the reduction of permanent AF are viewed by the table (Table 3). Altogether, the data of the study of Dernellis & Panaretou (Dernellis & Panaretou, 2004) provide highly significant evidence that a low-dose glucocorticoid therapy (i. e. 16 mg methylprednisolone for 4 weeks tapered to 4 mg for 4 months) compared to placebo ***excludes*** permanent AF (p(Prednisolone excludes AF) =0.99038462; X^2(Prednisolone excludes AF) = 0.0204) while the causal relationship was $k < 0$. In other words, the data as published by Dernellis & Panaretou (Dernellis & Panaretou, 2004) are not self-contradictory (Barukčić, 2018) and can be used for causal analysis too. The causal relationship between a therapy with (methyl) prednisolone and permanent AF is $k = - 0.3731$ while the exact p value (k) calculated by the hypergeometric distribution is p value (k) < 0.0001. The 95% CI (k) is -0.5924 until -0.1538, a highly significant result. In other words, there is a highly significant causal relationship between a low-dose glucocorticoid therapy (i. e. 16 mg methylprednisolone for 4 weeks tapered to 4 mg for 4 months) and the absence of permanent AF. A low-dose glucocorticoid therapy is highly effective against permanent AF and an "anti-dot" against permanent AF. **Q. e. d.**

4. Discussion

Much attention has been devoted in the past years to inflammation (Aviles et al., 2003; Anderson et al., 2004; Conway et al., 2004; Asselbergs et al., 2005) as the pathophysiological mechanism underlying the genesis of AF which has been reinforced even by experimental studies (Kirchhof et al., 2013). Still, the pathogenesis AF remains not even partially understood. The pathophysiology of AF is complex, but an inflammation itself can lead to a kind of "atrial myocarditis" with subsequent structural atrial changes resulting among other in AF (Korantzopoulos et al., 2003). Several *case studies* support this hypothesis. A 57-year-old patient with rheumatoid arthritis treated with a combination of etanercept and methotrexate developed a new-onset of atrial fibrillation after treatment for five months on this therapy (Wooten et al., 2000). As long as it appears justified to rely on the data as published by Hung et al. (Hung et al., 2017) *Etanercept* is effective against cytomegalovirus but not for sure against EBV. According to Barukčić et al. (Barukčić at al. 2018), EBV is the cause of rheumatoid arthritis (RA). Thus far, according to this case, it is highly improbable, that cytomegalovirus is a cause or the cause of atrial fibrillation. The incidence of myocarditis as a complication of an EBV infection is not so high (Takano et al., 2008). However, a chronic active Epstein-Barr virus (CAEBV) infection characterized by high EBV DNA levels in the peripheral blood (Kawabe et al., 2018) can cause organ damage demonstrated by endomyocardial biopsies with lymphocytic infiltration, necrosis of cardiomyocytes et cetera and end up in a chronic active myocarditis (Takano et al., 2008). Sometimes, an Epstein-Barr myocarditis (Antonakaki et al., 2016) is so severe that an urgent orthotopic heart transplantation is necessary. Finally, Aghenta et al. (Aghenta et al., 2008) published the case of *a 19-year-old healthy male patient* presented to hospital with clinical features of *infectious mononucleosis* (IM). Symptoms worsened despite therapy (ibuprofen, intravenous methylprednisolone, intravenous fluids et cetera). On day 2 of admission to hospital, electrocardiogram (ECG) showed *atrial fibrillation*. An Epstein Bar virus infection is able to cause a symptomatic atrial fibrillation (Aghenta et al., 2008) as a result of viral invasion. Judged solely in terms of logic, one single documented co-occurrence or co-incidence of an Epstein Bar virus infection and atrial fibrillation is of course not enough to provide a proof of a cause effect relationship between EBV and AF. It is very hard to make any sense of the case reported without supposing that EBV was the cause of AF of this 19-year-old healthy male patient. What is further remarkable about this case reported is that AF cannot be regarded any longer only as a health problem of those who are older.

It seems fair to say that the way in which other studies published support the EBV hypothesis with respect to AF is seemingly somewhat different. In the following, let us focuses heavily on the articulation and evaluation of some impressive rheumatoid arthritis studies. Very roughly, before examining these remarkable achievements in detail, to date, data are available which support the hypothesis that patients with rheumatoid arthritis have increased risk (Bacani et al., 2015) of atrial fibrillation. The incidence of atrial fibrillation (AF) among patients with rheumatoid arthritis (RA) compared to the entire Danish population was increased by a 40% (Lindhardsen et al., 2012). Bacani

et al. (Bacani et al., 2015) found that the incidence of AF even after adjustment for AF risk factors is increased in patients with RA. Epstein–Barr virus (EBV) is the cause of rheumatoid arthritis (Barukčić at al. 2018). Already we are very close to the core of the problem. In the first place, there is only one reasonable explanation for that consistency; it is very likely that Epstein–Barr virus (EBV) and atrial fibrillation are causally related. One difficulty with such an interpretation is of course even a relationship between EBV and RA is highly probable the same is not proved at a certain level of significance and it is necessary and good practice to stay calm and patient on this topic.

The Epstein–Barr virus (EBV) was discovered by electron microscopy of cells cultured from Burkitt's lymphoma tissue by Epstein et al. (Epstein et al., 1964) Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a gamma herpes virus which infects a large fraction of the human population. After the primary infection, EBV persists for life (Cohen, 2000) in memory B cells in the peripheral blood of human host while well controlled by host's immune system.

There is currently no treatment for removing EBV infections and very little success treating EBV infection with drugs. *Corticosteroids* are sometimes helpful. In the excellent paper, Dernellis and Panaretou (Dernellis & Panaretou, 2004) demonstrated that the use of low-dose Methylprednisolone successfully prevents recurrent and permanent AF.

Cell culture experiments support the thesis that *Vitamin D* may reduce the severity of viral infection by suppressing inflammation (Beardb et al., 2011).

Acyclovir with limited gastrointestinal absorption had no significant effect on EBV-related symptoms (Bissell et al., 1980) while *Valacyclovir* treatment in Epstein-Barr virus infection was effective (Lerner et al., 2007). Valacyclovir inhibits EBV *thymidine kinase* and is absorbed more efficiently from the gastrointestinal tract than acyclovir. Valacyclovir was not able to reduce infant CMV acquisition or breastmilk shedding of cytomegalovirus (Roxby et al., 2014) while EBV reactivation was decreased with valganciclovir prophylaxis (Gill et al., 2014).

The direct anti-viral activity of *ascorbic acid* (vitamin C, ascorbate) against herpes simplex virus type 1, influenza virus type A, picornaviridea virus 1, herpes simplex viruses (types 1 and 2), cytomegalovirus, parainfluenza virus type 2 and other viruses are documented in vitro (Furuya et al., 2008). Vitamin C deficiency is associated with viral infections (Chen et al., 2009). The clinical study of (Mikirova & Hunninghake, 2014) demonstrated that an intravenous administration of high dose ascorbate (IVC) therapy according to *Riordan IVC protocol* (Riordan et al., 2003; Mikirova et al., 2013) is able to reduce EBV EA IgG and EBV VCA IgM antibody levels over time. High-dose IVC infusions at the 7.5, 15, 25, and 50 gram dosages adjusted by plasma ascorbic acid levels attained post infusion and patients' tolerance lead to hemolysis in patients with *glucose-6-phosphate dehydrogenase (G6PD) deficiency*. Adding *magnesium* to high-dose IVC ascorbate infusions can help to reduce incidence of vein irritation and spasm.

Zinc (Zn) play a very important role in human immune system because of its pivotal role in the efficiency of modulating immune function (Mocchegiani & Muzzioli, 2000; Hirano et al., 2008). Zinc-deficient patients experience increased susceptibility to a variety of pathogens (Shankar & Prasad, 1998). Zinc supplementation may increase host resistance to infections. Arens and Travis (Arens and Travis, 2000) were able to inactivate herpes simplex virus (HSV) with zinc salts.

Despite good progress in the management of atrial fibrillation, AF remains one of the major causes of sudden death and morbidity in the world. For the patient, AF is associated with severe consequences such as stroke or death and other, while the direct costs of AF for the society are already extraordinary high (Stewart et al., 2004; Kim et al., 2011). In the year 2011, the US-AF costs have been estimated to range from $6.0 to $26.0 billion (Kim et al., 2011). The complexity underlying AF and the relative inefficacy of the currently available pharmacotherapy against AF requires and justifies the development of new treatment strategies to try to *cure* AF (Table 6).

5. Conclusion

Given the complexity of AF pathophysiology the findings of this study provide evidence of an impact of EBV infection on atrial fibrillation. Undoubtedly, the hypothesis: *without* EBV infection *no* AF remains to be elucidated and more systematic, regional studies of AF are required to better understand the relationship between an EBV infection and AF. At first sight, it seems hard to find one single patient with AF with a negative EBV serology.

Conflict of Interest

Author declare no conflict of interests for this article.

Acknowledgement

None.

Patient:

Table 6. Therapeutic schema to cure atrial fibrillation (experimental; not verified by trials; Don't use without doctor's advise!!!)

Drug	(Methyl-) **prednisolon**	**Cimetidin**	**Valacyclovir**	**Zinc-histidine**	**Vitamin C**	**Vitamin D** 20.000 I. U.	**Milk thistle** (silymarin)
Dosage	40 mg 1-0-0 a.c.	400 mg 1-0-1	500 mg 1-0-1	15 mg 0-1-0	1 g 0-1-0	1x1 per week	ca. 400 mg 0-1-0 daily
Week	(on 5 days per week)	a.c./c.c.	plus a lot of water !!!	p.c.	c.c./p.c.	(i.e. Sundays)	
1	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
2	-	x	x (7 days)	x	x	x	x
3	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
4	-	x	x (7 days)	x	x	x	x
5	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
6	-	x	x (7 days)	x	x	x	x
7	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
8	-	x	x (7 days)	x	x	x	x
9	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
12	-	x	x (7 days)	x	x	x	x
11	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
12	-	x	x (7 days)	x	x	x	x
13	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
14	-	x	x (7 days)	x	x	x	x
15	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
16	-	x	x (7 days)	x	x	x	x
17	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
18	-	x	x (7 days)	x	x	x	x
19	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
20	-	x	x (7 days)	x	x	x	x
21	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
22	-	x	x (7 days)	x	x	x	x
23	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
24	-	x	x (7 days)	x	x	x	x
26	x (Mo, Tue, Wen, Thur, Fri)	x	-	x	x	x	x
26	-	x	x (7 days)	x	x	x	x

The drugs taken are cancelled. "x" denotes the necessity of taking the drug, "-" denotes the necessity not to take the drug. Start of therapy on.

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