

Mini Review

Cardiovascular risk factors in centenarians

Antonio Galioto, Ligia J. Dominguez, Antonella Pineo, Anna Ferlisi, Ernesto Putignano, Mario Belvedere, Giuseppe Costanza, Mario Barbagallo *

Geriatric Section, Department of Internal Medicine and Emerging Pathologies, University of Palermo, Viale Fco. Scaduto 6/c, 90144 Palermo, Italy

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Abstract

Several studies have shown that centenarians have better cardiovascular risk profiles compared to younger old people. Some reports have revealed that cardiovascular diseases (i.e. hypertension, diabetes, angina and/or myocardial infarction) are less common in centenarians respect to 70 and 80 years old persons. In order to explain this evidence, there is a growing number of hypothesis that consider a combination of genetic factors and lifestyle aspects to elucidate the exceptional longevity of centenarians, able to overcome the most frequent mortality cause, which is a cardiovascular event. It has been suggested that a role on this better cardiovascular risk profile may be played by the increasing use of pharmacologic treatments in the elderly population (specially for hypertension and dyslipidemia), but the contribution of drug treatments to promote extreme longevity is not confirmed. Furthermore, centenarians in general have needed fewer drugs at younger ages due to a healthy lifestyle. The importance of the genetic contribution is demonstrated by the inheritance of low-risk cardiovascular profiles in centenarian offspring and lower prevalence of cardiovascular diseases in this population as compared with their spouses or with age-matched subjects without centenarian parents. Another advantage in centenarians' offspring seems to be a delay in the onset for cardiovascular diseases, respect to age- and sex-matched controls.

Cardiovascular risk factors mirror the factors that contribute to longevity. Hence, it is not surprising that these risk factors are less prevalent in centenarians when compared to younger old individuals.

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1. Introduction

Among older population, centenarians may be considered the best example of successful cardiovascular aging. The capacity to avoid, delay or limit cardiovascular damage associated with aging-related diseases has been proposed as one of the mechanisms that may help to explain the successful aging in centenarians. In particular, lower incidence of cardiovascular diseases has been observed in centenarians, which represent the most frequent causes of death at younger ages (70–80 years). As such, in a study on US elderly Veterans, 93 centenarians had a lower prevalence of hypertension, angina or myocardial infarction and diabetes compared to Veterans aged 85–99 years

(Selim et al., 2005). The examination of death certificates has shown a decreased frequency of diabetes and myocardial infarction as causes of death in centenarians in contrast with the accepted concept that atherosclerosis and congestive heart failure increase in frequency with age (Gessert et al., 2002). These findings suggest that centenarians appear to “outlive” the cardiovascular risk factors for many of the conditions that are frequent causes of death at the age of 70, 80, or 90 years. As such, in a study conducted on healthy centenarians from Okinawa, pulse wave velocity (an index of arterial wall flexibility) was generally in the lower range, below 10 m/s, which is comparable to those observed at a younger age (Suzuki et al., 2001). In this special population, better lipid profiles have been documented as well (see below, Barter, 2004).

The advantages of a favorable cardiovascular risk profile in centenarians seem to be transmitted to their descen-

* Corresponding author. Tel.: +39 091 6552885; fax: +39 091 6552952.
E-mail address: mabar@unipa.it (M. Barbagallo).

dants, who exhibit better cardiovascular risk profiles compared to age-matched people without centenarian relatives (Perls and Terry, 2003). This supports the existence of genetic determinants in the genesis of arteriosclerosis and its complications. In addition, a more favorable inflammatory atherogenic profile has been reported in centenarians together with a better antioxidant profile (Fletcher et al., 2003), which is in accordance with the inflammatory and oxidative stress hypothesis of cardiovascular aging (Chung et al., 2001).

Together with a favorable genetic profile, a key aspect that seems to be present in most of those who have reached an exceptional old age is to have conducted a healthy lifestyle (Perls and Terry, 2003). Indeed, several reports have documented that centenarians commonly have followed a series of “good habits” initiating at younger age. Particular interest is directed currently to the effects of caloric restriction, no smoking history, moderate intake of alcohol and abundant intake of vegetables rich in antioxidant substances, all of which seem to correlate positively with the achievement of longevity in genetically predisposed individuals (Perls and Terry, 2003).

2. Hypertension in centenarians

Hypertension, a very common problem in older persons, represents the most frequent risk factor for cardiovascular and cerebrovascular morbidity and mortality (Chobanian et al., 2003; Barbagallo et al., 2002). The most powerful risk factor for death, cardiovascular death and hypertension in large populations is age (Prospective Studies Collaborative, 2002). Therefore, it is not surprising that the lifetime risk of developing hypertension among adults (55–65 years old individuals) was over 90% in the Framingham Study (Vasan et al., 2002). In the same study, isolated systolic hypertension was the most common form of hypertension in older people, accounting for 60% of the cases (Kannel, 1996). Furthermore, the systolic and pulse pressures may be the major predictor of outcome in the elderly (Franklin, 2006).

Interestingly, although there are no definite data on hypertension in centenarians, available data suggest that hypertension is less prevalent in centenarians compared to younger old individuals, in contrast with the evidence of increasing blood pressure values with age. A study performed in eight centenarians disclosed that only two of them had systolic hypertension (Righi et al., 1993). An Italian study including 73 centenarians from Calabria confirmed that even in the presence of a progressive increase in blood pressure with age, this trend was not found in centenarians with only 14 centenarians (19.2%) being hypertensive. The authors stressed the possible role of genetic determinants but especially of lifestyle and dietary habits of the 73 centenarians enrolled (Gareri et al., 1996). Thus, although it cannot be excluded that very old age is accompanied by a decrease in blood pressure, it appears reasonable that a favorable genetic profile and/or a healthy

lifestyle that protect from blood pressure elevations also protect from premature cardiovascular death.

Bertinieri et al. studied a group of 16 centenarians without history, signs or symptoms of cardiovascular or non-cardiovascular diseases and with no drug treatment compared to 20 and 80 years old persons measuring 24 h blood pressure means and profiles. In the centenarian group, blood pressure and heart rate values were similar during daytime and nighttime. Moreover, 24 h blood pressure values in centenarians were slightly lower than in subjects aged 80 years (Bertinieri et al., 2002). Another study performed in longevous subjects and their progeny confirmed that these individuals had a diastolic daily mean level lower than expected, according to the age-related blood pressure increasing trend observed in the common population. Both, children and grandchildren of the longevous subjects had a systolic and diastolic daily mean level significantly lower than their coeval subjects of the general population (Cugini et al., 1998).

It is well documented that antihypertensive treatment in older hypertensive persons (up to the age of 80 years) with systo-diastolic or isolated systolic hypertension reduces cardiovascular events and cardiovascular mortality (Chobanian et al., 2003). However, in the very old (80 years or older), the evidence is scarce and less convincing (Goodwin, 2003; Franklin, 2006). At present, there are no significant data on the benefit of drug treatment for blood pressure elevation in centenarians. The data available on the effects of lowering blood lipids with therapy in the elderly as well as in centenarians are scarce and contrasting, as will be discussed below (Beckett et al., 2000).

3. Lipid profiles

Elevated cholesterol levels are common in over-65 years old people (61% of women aged 65–74 years have total cholesterol levels >240 mg/dL) (Beckett et al., 2000). However, it has been suggested that after 65 years, increased blood lipids, although still a risk factor for coronary heart disease, become less pronounced as a risk factor and that by 75 years their predictive value has disappeared. Indeed, in the very elderly, there is evidence to suggest that high total cholesterol is associated with longevity (Weverling-Rijnsburger et al., 1997; Beckett et al., 2000). These results do not necessarily contradict the advantages of lowering blood cholesterol levels in very old people. It is possible that elevated cholesterol levels are not directly associated with longevity, but rather low cholesterol levels may be associated with chronic diseases or malnutrition, as shown in epidemiological studies in older populations. In addition, lower cholesterol levels in the very old populations may be attributed to a selection of the population due to the premature death of hypercholesterolemic individuals. Thus, subjects with dyslipidemia very rarely reach extreme old age (Motta et al., 1998). However, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), the first trial to specifically evaluate the benefits of statins

on vascular risk in an elderly population, showed a reduction in the risk of coronary heart disease in elderly individuals, extending the possible benefits of statin treatment to older populations (Shepherd, 2003).

Several reports in centenarians have suggested that this selected population have a protective lipid profile phenotype against atherosclerosis-related diseases. A Japanese study has shown lower levels of total cholesterol (TC) and low-density lipoprotein cholesterol in centenarians versus septuagenarian controls (Suzuki et al., 2001). The favorable lipids and lipoprotein profile in centenarians has been confirmed by other authors in diverse populations. An Italian multicentric study found low average TC and triglycerides in centenarians, and mean high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-1 in the normal upper range, compatible with longevity and with the lower prevalence of atherothrombotic diseases in these extreme longevous individuals (The Italian Multicentric Study on Centenarians, 1998). In particular HDL-C seems to be directly correlated with free cardiovascular disease longevity, in accordance with the role of this lipoprotein in several anti-atherogenic mechanisms (i.e. promotion of increased production of endothelial nitric oxide). Low levels of HDL-C have been shown to be a powerful predictor of premature coronary heart disease and stroke in human prospective population studies. Evidence of the protective properties of HDL-C has been as well documented in older people and their offspring (Barter, 2004), suggesting the importance of promoting lifestyle strategies (see below) to raise HDL-C levels in older persons.

4. Cardiovascular disease in centenarians' offspring

For centenarians to achieve their exceptional longevity, they need not only to have a genetic/environmental protection for cardiovascular diseases-related death, but also against all other premature mortality causes, first of all cancer. The inheritance of the capacity of outlive the cardiovascular risks seem to be also present in centenarians' offspring. These subjects have markedly reduced relative risks for age-related diseases, particularly heart disease, hypertension and diabetes, and they represent a model for study the slowly aging relative to the general population and the delay and perhaps escape from important age-related diseases (Perls and Terry, 2003). A cross-sectional study has demonstrated a 62% reduction in all-cause mortality, and an 85% lower coronary heart disease-specific mortality in centenarians' offspring (Terry et al., 2004a). The offspring of long-lived parents had significantly lower prevalence of hypertension (–23%), diabetes mellitus (–50%), heart attacks (–60%) and strokes than several age-matched control groups (Atzmon et al., 2004). The New England Centenarian study has shown that centenarian offspring have a 56% reduced relative prevalence of heart disease, a 66% reduced relative prevalence of hypertension, and a 59% reduced relative prevalence of diabetes (Terry et al., 2003). It has also been shown that the median

ages of onset for coronary heart disease, hypertension, diabetes and stroke, are significantly delayed in centenarian offspring by 5.0, 2.0, 8.5 and 8.5 years, respectively, compared with age-matched controls (Terry, 2004b).

5. Inflammation, cardiovascular disease and longevity

The incidence of atherosclerosis is markedly linked to the presence of a pro-inflammatory status (Viles-Gonzalez et al., 2006). Thus, control of inflammatory reactions may also decrease the incidence of cardiovascular diseases. Gene polymorphisms for pro-inflammatory cytokines seem to contribute significantly to the risk of atherosclerosis-related diseases (Candore et al., 2006a; Lio et al., 2004). The linkage between inflammation, genetic factors and atherosclerosis has been demonstrated by the analysis of the frequency of pro-inflammatory and anti-inflammatory genotypes in Italian centenarians. In this population, the frequency of the genotype associated with interleukin 10 (–1082GG) is related to a significant increased production of this anti-inflammatory cytokine. Conversely, the frequency of the genotype associated with low production of interleukin 10 is significantly higher in patients with acute myocardial infarction compared to controls. Although a low production of interleukin 10 is associated with an increased resistance to pathogens, increased concentrations of this cytokine seems to be linked to a better control of inflammatory responses induced by chronic vessel damage, and with a reduced risk for atherogenic complications (Lio et al., 2004). It has been suggested that different genotypes of inflammatory molecules (pro- and anti-inflammatory cytokines) may have opposite effects on predisposing to atherosclerosis and accelerated vascular aging or longevity (Candore et al., 2006a).

Pro-atherogenic effects of chronic infections (i.e. *Helicobacter pylori*, *Chlamydia pneumoniae*, HCV, CMV) seem to be mediated by the pro-inflammatory cytokine tumor necrosis factor (TNF) α , which has been associated to the development of cardiovascular disease. Although TNF α is likely to be involved in the pathogenesis of atherosclerosis, a Danish study of 126 centenarians did not confirm the link for TNF α , chronic *C. pneumoniae* infection and cardiovascular diseases in centenarians (Bruunsgaard et al., 2002). It has been proposed that a “lower infectious burden” is an important predisposing factor to achieve extreme longevity, that is, an increased chance of long life is more likely in an environment with a reduced load of external antigens (Lio et al., 2004). Thus, people who are genetically predisposed to have a weak inflammatory activity (lower IL-6 pro-inflammatory action), seem to have fewer chances of developing atherosclerosis and cardiovascular disease, and, consequently, to live longer (Candore et al., 2006b). In a study involving 126 centenarians, higher concentrations of TNF α (that initiates the cytokine cascade) were associated with both Alzheimer's disease and generalized atherosclerosis (Bruunsgaard et al., 1999). The same authors have shown a direct correlation between

elevated levels of TNF α and mortality in centenarian men and women suggesting that TNF α is an independent prognostic marker for mortality in centenarians and a possible marker of frailty in the very elderly (Bruunsgaard et al., 2003).

Numerous studies have demonstrated that oxidative stress is the promoter of a series of progressive and irreversible alterations of the arterial wall (i.e. endothelial dysfunction, intima-media thickening) that promote inflammation and end up in the development of atherosclerosis. To combat the harmful effects of free radical species of oxygen, antioxidant enzymes play an essential role. In a Japanese study in which lipid peroxide (one of the main free radical by-products) was measured in centenarians and in septuagenarian controls, the level of this free radical product was significantly lower in centenarians respect to controls (Suzuki et al., 2001). A Danish study performed on 41 centenarians evaluated the activity of antioxidant enzymes superoxide dismutase, glutathione peroxidase, catalase and glutathione reductase in erythrocytes. In centenarians superoxide dismutase activity was decreased, suggesting a reduced demand at lower metabolic rate and oxygen consumption. Conversely, an elevated activity of glutathione reductase was observed in centenarians, which may be linked to their better survival versus younger controls (Andersen et al., 1998).

Several other candidate genes with variants associated with longevity have been studied. Those specifically related to cardiovascular disease include genes encoding apolipoprotein E (APOE)4, APOE2 (Lewis and Brunner, 2004), APOC3 (Atzmon et al., 2006), microsomal triglyceride transfer protein (MTTP) (Geesaman et al., 2003; Nebel et al., 2005; Bathum et al., 2005), and angiotensin I-converting enzyme (ACE) (Luft, 1999; Bladbjerg et al., 1999; Blanche et al., 2001).

Apolipoprotein E (APOE), a ligand for the LDL receptor, has three isoforms, APOE2, APOE3 and APOE4, which are encoded by different alleles and interact differently with specific lipoprotein receptors that alter cholesterol circulating levels. APOE4 has been consistently associated with a moderately increased risk for cardiovascular risk and Alzheimer's disease while APOE2 seems protective for these pathologies (Lewis and Brunner, 2004). Furthermore, individuals with atherosclerosis, peripheral vascular disease or diabetes mellitus have a higher risk of cognitive decline if they carry the APOE4 variant (Haan et al., 1999). Although APOE4 frequency varies significantly among younger adults, in the same populations the frequency in centenarians is about half in each population. However, the estimated mortality risk variation for carriers of APOE4 and APOE2 versus APOE3 is small which means that it may not be considered a longevity gene, rather a gene that slightly influences yearly mortality (Bathum et al., 2006). A recent study showed that the 641C allele in the APOC3 promoter is present more frequently in American Ashkenazi Jewish centenarians and their offspring compared with controls, associated with a favorable

risk profile and survival (Atzmon et al., 2006). This study needs replication in other populations.

Geesaman et al. in a recent study suggested that MTTP, a protein involved in lipoprotein metabolism, is implicated in longevity, since it would be responsible for a linkage for longevity found in chromosome 4 (Geesaman et al., 2003). However, two rigorous studies in Germany (Nebel et al., 2005) and Denmark (Bathum et al., 2005) failed to confirm this association.

Another plausible candidate gene for longevity is ACE gene, since this enzyme has been associated with cardiovascular and renal diseases. A German study found an increased frequency of homozygosity for one ACE allele in octogenarians (Luft, 1999). However, this finding could not be confirmed in two large studies of centenarians (Bladbjerg et al., 1999; Blanche et al., 2001).

6. Lifestyle, cardiovascular disease and longevity

Currently, there is increasing evidence of modifiable factors that contribute to the possibility that an individual with genetic predisposition can reach extreme longevity. It is now widely accepted that aging is the result of the sum of damage during the course of life, with consequent alterations in several functions of the organism that may favor the development of diseases such as cardiovascular disease, accelerating aging and mortality (Bokov et al., 2004). This concept has led to seek for factors that may reduce or combat the cellular damage or enhance the repair mechanisms, hence, delaying the beginning of disease and improving the quality of life during old age. There is growing evidence that it is possible to improve quality of life and delay cardiovascular aging of older persons by following some lifestyle-related rules (i.e. diet, physical activity, smoking) (Perls and Terry, 2003).

Most of the centenarians have followed a healthy lifestyle in regard to (a) smoking, (b) diet and (c) physical activity (see below) and are perhaps the best example of the influence of lifestyle factors on cardiovascular disease and on longevity.

6.1. Smoking

Cigarette smoking has been linked to the most common causes of death in older persons including cardiovascular events (Bratzler et al., 2002). Although smoking is not incompatible with the achievement of old age, centenarians who had never smoked exhibited benefits in terms of quality of life and mortality in an Italian study. This study, that included 157 centenarians, showed a lower survival rate in smokers (20.7 ± 11.2 months) than in non-smokers centenarians (27.0 ± 19.0 months), and suggests an incompatibility between smoking and successful aging (Tafano et al., 2004). In vitro studies have demonstrated direct effects of smoke extract on cellular senescence: fibroblast exposed to smoke extracts stopped proliferation and up-regulated p53 and p16 retinoblastoma protein, pathways

that are linked to cellular senescence (Nyunoya et al., 2006).

6.2. Diet

Several studies have investigated nutrition habits in centenarians since dietary factors have been proposed as key determinants in the achievement of extreme longevity in genetically predisposed individuals (Perls and Terry, 2003). The Japanese region of Okinawa has one of the world's highest concentrations of centenarians, with the world's longest life expectancy for any country or state. Older people from Okinawa have better cardiovascular risk profiles (i.e. low cholesterol, low homocysteine levels) when compared to other Western countries and high blood pressure was recognized in only 1.5% of apparently healthy centenarian subjects. Most of the persons in this population never developed a taste for salt and, perhaps in relation to this, their heart disease and stroke rates are much lower than the Japanese average (Suzuki et al., 2001). This population also has a reduced risk for coronary heart disease (up to 80% lower than Western populations). There is little doubt that the cardiovascular protection of Okinawan centenarians is linked to their exceptional healthy lifestyle including a low-caloric diet, plenty of fish and vegetables and very low in fat and salt content, accompanied by regular exercise (see below), moderate alcohol use, avoidance of smoking, and a stress-minimizing psycho-spiritual outlook (Suzuki et al., 2001). In accordance with the proposed effect of caloric restriction on longevity (Sohal and Weindruch, 1996), the low-caloric intake of Okinawans has been related to their long life expectancy (Weindruch and Sohal, 1997). Okinawan elders are lean (average body mass index of 18–22) and stay lean by eating a low-caloric diet, based on unrefined-complex carbohydrates, due to a cultural habit known as “hara hachi bu”, that is, only eating until they are ~80% full. Caloric restriction has been shown to attenuate both the degree of oxidative damage with aging and the associated decline in function in experimental animals (Sohal and Weindruch, 1996). An increased body of evidence suggests that the accumulation of oxidative damage of macromolecules plays a major role in aging and diseases of aging also in humans. The lower levels of lipid peroxide reported in Okinawan elders are compelling evidence that they suffer less free radical-induced damage (Suzuki et al., 2001). Not only low-caloric intake may decrease free radical production and oxidative stress-induced damage, but also the consumption of antioxidants with the diet may combat oxidative stress. However, it is worth mentioning that these populations may differ from those of the Western world, concerning not only their life style, but most likely also their genetic background. Therefore, it cannot be definitely asserted that the same observations in similar conditions may occur in populations of different ethnical/genetic background.

Numerous studies have shown that Mediterranean dietary pattern, characterized by food particularly rich in anti-

oxidants (olive oil, fresh vegetables, fruits, wine in moderate amount), is associated with a decreased cardiovascular mortality (Knoops et al., 2004; Trichopoulou et al., 2005; Trichopoulou and Critselis, 2004; Rimm and Stampfer, 2004; Kok and Kromhout, 2004; Trichopoulou et al., 2003; Hu, 2003; Covas et al., 2002; Kris-Etherton et al., 2001) and with a reduced risk of dyslipidemia among older people (Polychronopoulos et al., 2005). The Survey in Europe on Nutrition and the Elderly, a Concerted Action (SENECA) investigated the relation between plasmatic concentration of antioxidants (carotene and α -tocopherol) and mortality in 1168 elderly subjects. High plasma carotene levels were associated with lower mortality risk for cardiovascular diseases with the lowest risk in those with a body mass index <25 kg/m² (Buijsse et al., 2005). A study conducted on 1214 participants aged 75–84 years found a marked inverse correlation between plasma ascorbate concentrations and all-cause and cardiovascular mortality (Fletcher et al., 2003). Johnson et al. reported that although the consumption of most nutrients were similar among 60-, 80- and 100-year-old community-dwelling groups, centenarians tended to consume about 20–30% more carotenoids and vitamin A from foods (Johnson et al., 1995).

A study on alimentary habits in centenarians from Tokyo compared the food intake of centenarians, octogenarians and younger subjects in Tokyo metropolitan area. The nutritional intake in centenarians and octogenarians in 1995 was 60% and 75% that of control young persons. However, there was a similar nutritional intake in well-nourished centenarians and in octogenarians. Interestingly, the authors noted a difference in dietary habits between centenarians in 1981 and their 1995 counterparts, with the former having higher consumption of cereals, eggs, algae products and legumes compared to the later (Takeda et al., 1998). Another important study of longevity and survival of the oldest old is the Georgia Centenarian Study that is currently ongoing and will be concluded in 2007. Preliminary data from this study show the tendency of healthy habits in centenarians, thus confirming their role in the achievement of extreme longevity (Nickols-Richardson et al., 1996; Quin et al., 1997). Among centenarians enrolled in this study, only few smoke, were obese, or consume excessive alcohol and most remain active throughout their life.

6.3. Physical activity

Several studies have shown the key role of conducting a physical active life to avoid cardiovascular disease and reach very old ages. A Finnish prospective 16-year follow-up study investigated the relationship between physical inactivity, in terms of leisure time physical activity (LTPA), and cardiovascular mortality, in middle-aged and elderly men and women. Compared with the most active subjects, men and women with no weekly vigorous activity had higher relative risk for cardiovascular mortality, highlight-

ing the protective effect of LTPA in obese and non-obese, men and women, fit and unfit subjects (Malmberg et al., 2000).

Several studies had shown that dietary patterns and lifestyle factors are associated with mortality from all causes, coronary heart disease, other cardiovascular diseases and cancer, but few studies had investigated these factors in combination. The HALE project (Healthy Aging a Longitudinal Study in Europe) evaluated 10-year mortality from all causes in a group of 1507 apparently healthy men and 832 women, aged 70–90 years in 11 European countries. This study concluded that a combination of the adherence to a Mediterranean diet together with a healthful lifestyle (physical activity, moderate alcohol use and non-smoking) is associated with over 50% lower rates of all-causes and cause-specific mortality (Knoops et al., 2004).

7. Conclusions

Centenarians represent the best example of cardiovascular successful aging. By definition, they have been able to overcome cardiovascular fatal events at a younger age. Genetic and environmental factors are interconnected aspects responsible for the better cardiovascular profile observed in centenarians. The lower cardiovascular burden of centenarians' siblings gives evidence of genetic determinants of cardiovascular longevity. On the other hand, numerous studies in diverse populations confirm that a healthy lifestyle plays a fundamental role as well. These facts, at a glance, may suggest that centenarians are “cardiovascular disease” free, but unfortunately this is not the case. Nevertheless, although centenarians may develop cardiovascular diseases as their 70 and 80 years old counterparts (i.e. hypertension, stroke, coronary events), they have a better survival and a better capacity to overcome the damage (primarily death and disability) provoked by cardiovascular diseases. Among the possible mechanisms that can help to explain the better cardiovascular profiles of some cluster of centenarians, the capacity to produce a lower pro-atherogenic inflammatory response to chronic infective stimuli, as well as the ability to develop a better antioxidant response to oxidative stress damage of the arterial wall, may be considered. These features may help to explain the better cardiovascular survival of centenarians respect to younger populations.

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