

# How Do You Stay Young At Heart?

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Progressive ageing is unfortunately associated with an increasing risk of developing health problems. Statistically one of the most common medical conditions afflicting the elderly is heart disease,[1] second only to arthritis as the most prevalent medical condition affecting the elderly. Much is known, discussed, and broadly acted upon, regarding the many modifiable risk factors for heart disease such as blood pressure, cholesterol, weight and smoking, however the largest risk factor for heart disease is not normally referred to – increasing age. In our opinion this is perhaps because this risk factor is considered un-modifiable and unavailable for commercial exploitation – yet. Nevertheless, there may be opportunities on the horizon and perhaps further consideration should be given to how to combat this dominating risk factor for cardiovascular problems.

Heart disease is a broad term frequently used to cover all dysfunction of the cardiovascular system. However many changes occur in the cardiovascular system of elderly individuals in a sub-clinical but progressive manner which are more commonly associated with pathology. This sub-clinical accumulation of defects appears to progress steadily throughout the lifespan until they become sufficient to produce clinical dysfunction and symptoms leading to a diagnosis of heart disease.[2] Such changes include both structural remodelling and functional alterations.

## ***Problems of the Ageing Cardiovascular System***

Common problems of the cardiovascular system afflicting the elderly are (Figure 1):

- ‘Hardening’ of the arteries due to calcification and remodelling of the arterial wall. This leads to increased vascular resistance, increased blood pressure and an increased work load on the heart.[3, 4]

- Decreased relaxation and an increased stiffness of the heart muscle itself. Remodelling of the extracellular matrix of the heart is associated with reduced compliance limiting cardiac capacity, decreasing maximal output and again increasing the workload on the heart.[5, 6]
- Impaired coronary circulation. Atherosclerotic plaques accumulate in the arteries of the cardiovascular system including those supplying the heart with blood in an age and other risk-factor dependent manner (particularly associated with cholesterol).[7] As they enlarge and/or rupture causing clots to form the oxygen supply to the heart is compromised and cardiac damage is likely to occur. Increasingly people survive such heart attacks, but the diminished function of the damaged heart often means the remaining life of these individuals is associated with significantly curtailed exercise capacity.
- Impaired peripheral circulation. What affects the coronary arteries also affects all other arteries and atherosclerotic plaques accumulate in the peripheral vasculature with age. When plaques enlarge or rupture creating clots in the limbs or cerebral vasculature the associated limb or organ is in danger. Intermittent claudication is pain in the limbs normally associated with exertion in the elderly but due to impaired circulation to a limb causing insufficiency in oxygen supply.[8] The associated intolerance to exercise contributes significantly to immobility in the elderly and can lead to loss of limbs in a worst case scenario. Similarly if atherosclerosis affects the cerebral vasculature stroke is likely with its associated problems and diminished oxygen supply to the brain is also associated with an early onset of dementia and other disorders of neural function.
- Pacemaker dysfunction. The normal pacemaker of the heart, the sinoatrial node shows an age-dependent deterioration in its ability to operate at high frequencies and to control the beating rate of the heart. The majority of pacemaker dysfunction occurs in the elderly increasing in incidence in an age-dependent manner. Untreated this condition predisposes to fainting, cardiac arrhythmias, stroke, sudden death and exercise intolerance.[9] With age the sinoatrial node progressively loses proteins required for the heart beat to be

initiated and for this electrical signal to propagate down the heart causing normal activation.[10, 11] This inactivation and disconnection of the heart's own pacemaker requires treatment by implantation of an artificial one and over 70% of such implants are made in those over 65 years of age.[12]

- Inability to respond to stress. Cardiac capacity has therefore fallen, the work load on the heart has increased and the ability of the pacemaker to provide a high activation frequency has fallen so it is no surprise to find the heart cannot respond to stress very well. The normal response to cardiovascular stress such as exercise is to release nor-adrenaline and adrenaline which acts on adrenergic receptors on the heart causing the contractile strength to increase and the heart rate to accelerate. In the aged heart however this response is significantly blunted limiting the ability to respond to stress.[13, 14] Key factors behind this seem to be a desensitisation of the adrenergic receptors on the heart and a decline in the ability to generate the normal signal associated with stimulation of these receptors.
- Increased susceptibility to damage. The aged heart is more likely to be subjected to ischemia or increased operational stresses due to the changes outlined above but unfortunately with age the heart loses its ability to resist damage in the event of such stresses. Comparable levels of ischemia, hypoxia, or even simple increases in stimulation by adrenaline, which can be tolerated by the young heart can cause considerable damage in the old heart causing cell death or disorganised activation of the heart (arrhythmias).[15] This appears to be due to a loss of the protective arrangements that guard the heart from damage although the precise mechanisms are still controversial. Changes in heat shock proteins, mitochondria and ion channels are all implicated in this age-associated decline in tolerance but the precise interplay and how this may change with age is still being worked out.

Following this sobering list of reasons why the aged cardiovascular system is likely to become a dysfunctional cardiovascular system the natural question arising is how can we intervene to improve the outlook for those old at heart? Much has been written regarding the benefits of modifying a variety of risk factors, e.g. high blood

pressure and cholesterol, and how these can limit the risk of heart attack. However whilst these interventions can prevent problems associated with ischemia and blockage of the vasculature avoiding a test of the weakened ability to resist damage what influence do they have on the background problem of ageing of the cardiovascular system? Changes such as the development of pacemaker dysfunction, intolerance and inability to respond to stress, and a decline in the maximal cardiac output appear to occur whether you follow a healthy diet or not, so what should we do to tackle the underlying issues of the ageing cardiovascular system?

### ***Preserving Healthy Function in the Ageing Cardiovascular System***

Exercise is frequently advocated as a way to improve cardiovascular health and for several key areas there is plenty of evidence suggesting this is true. Exercise beneficially modifies cholesterol profiles potentially limiting atherosclerosis,[16] it can help lower blood pressure and weight,[17] limiting baseline cardiovascular stress, and it improves the heart's ability to withstand acute stress such as ischemia.[18] As such regular exercise increases the likelihood of living to an older age extending mean lifespan (although not maximal lifespan),[19] but what direct effects does it have on the ageing of the heart?

Here despite some studies showing that exercise can prevent age-associated changes in gene expression within the heart the evidence becomes slightly disappointing.[20] Masters athletes who have trained intensively throughout their life, still experience a fall in maximal achievable heart rate, and maximal cardiac output.[21] Although there is evidence that this fall is not as rapid as that seen in sedentary individuals. A more surprising finding is that people who have performed intensive endurance exercise throughout their life (e.g. competitive marathon runners and cyclists) are actually more likely to suffer from cardiac pacemaker dysfunction and arrhythmias and require an artificial pacemaker in later life than those who have led a relatively sedentary existence [22, 23], leading us to question whether exercise (or certainly intensive exercise) is an ideal solution for healthy ageing of the heart?

So what other solutions are there for an ageing cardiovascular system? Diet is frequently considered as an important modifier of cardiovascular stress and the atherosclerotic process. By keeping salt low in the diet blood pressure and hence cardiovascular stress can be limited. Cholesterol has become one of the most popular modifiable risk factors for atherosclerosis to be targeted by a variety of campaigns in recent times. It is now well established that keeping cholesterol low associates with slower development of atherosclerosis and reduced incidence of coronary heart disease and the widely-prescribed statin family of drugs target this relationship (although arguably not as well as diet can – but with less effort). Much remains to be characterised regarding the formation of atherosclerotic plaques though and the precise blood lipid components posing the greatest danger or benefit, with debates continuing regarding the relative use of measures of LDL (low-density lipoproteins), HDL (high-density lipoproteins), their sub-components, and their ratio as predictors of heart disease. One thing that is clear though is that low LDL and high HDL cholesterol are generally optimum for preventing atherosclerosis.

As a separate consideration of diet there is a tendency for the elderly to consume a diet of poorer nutritional quality and suffer from deficiencies of some vitamins and minerals. Much has been made of the potential benefits of vitamin E or C supplementation to preserve cardiovascular function in the elderly and guard against the potential oxidative stress of ageing or even cardiac ischemic damage. Such supplementation trials and studies however show very mixed success and data with potential beneficial effects in populations that may have already had deficiencies but unfortunately there is no clear sign that large anti-oxidant vitamin supplementation or consumption will prevent cardiovascular disease or mortality from such causes. The more interesting area of work at the moment in this area is actually on vitamin D where a link between vitamin D deficiency and cardiovascular risk has been established.[24] In the elderly vitamin D absorption and synthesis appears to be impaired and due to mobility issues exposure to sunlight can be reduced. This offers therefore not only a risk factor for osteoporosis with ageing but also apparently the risk of cardiovascular disease. The precise mechanisms why vitamin D deficiency should be so problematical for the cardiovascular system are unclear but may include reductions in blood pressure.[25] Some studies have already questioned whether vitamin D supplementation may help healthy ageing in the elderly with mixed results,

perhaps because overly-high vitamin D levels, can actually be a risk factor itself, but more are likely to follow to establish if this is a route to healthy cardiovascular ageing.

Diet also impacts body weight, itself a risk factor for cardiovascular disease, and with caloric restriction being one of the very few interventions known to consistently increase maximal lifespan a careful eye on calories consumption is perhaps warranted. In animal models and humans on caloric restricted regimes cholesterol, bodyweight, blood pressure and resting glucose levels fall (all important cardiovascular disease risk factors) but perhaps more surprisingly cardiac tolerance to ischemia increases.[26] As such caloric restriction offers many of the advantages of exercise for the cardiovascular system and heart itself, but encouraging participation in either is difficult! Interestingly the effects of exercise and caloric restriction may also be additive and of benefit later in life with one study showing complete restoration of protection against ischemia in elderly animals when exercise and caloric restriction were combined.[27]

On balance it appears regular exercise and/or caloric restriction make it more likely you will get to experience more of the ageing process by reducing mortality projections (and not just death through cardiovascular-related causes) but they do not prevent ageing, and in some cases may actually increase the occurrence of age-associated cardiac issues. Much work however remains to be done to investigate the fine detail of the ageing cardiovascular system. The recent findings that even the adult heart can have progenitor cells embedded within it capable of dividing into new cardiac cells offers new hope for renewing the ageing heart keeping it youthful in function and operation.[28] The bad news is we appear to lose these progenitor cells as we age and they also become reticent to act, divide and repair damage in later life. Restoration of the activity of these progenitor cells and re-establishing the heart's ability to repair itself is perhaps one of the most exciting future prospects for ensuring healthy cardiac function for all in old age. Recent work has suggested that elevated levels of IGF-1, such as can be stimulated by exercise, are important for keeping progenitor cells active into old age and can extend lifespan.[29]

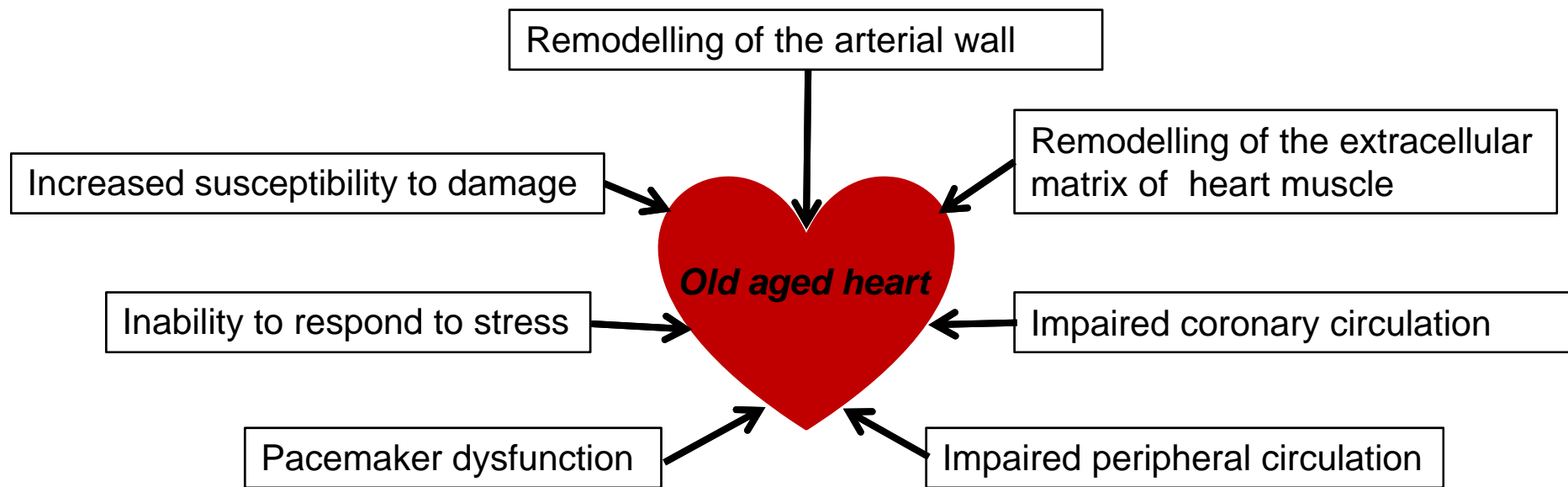
### ***A Prescription for Healthy Ageing of the Cardiovascular System***

Until we understand more about how the cardiovascular system ages and how to keep it youthful the best advice is keep blood pressure and LDL cholesterol down,[30, 31] keep vitamin D,[24] HDL cholesterol and IGF-1 up,[32, 33], keep body weight and caloric intake down and stay active with exercise most days of the week.[34] These interventions may not prevent ageing entirely but will increase the chances of a healthy longer life (on-average) and sounds like a good excuse for regular steady 30 minute runs in the sun - a prescription which will impact many of these factors.

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**Figure 1: Problems of the Ageing Cardiovascular System**

Contributing factors to dysfunction of the cardiovascular system in the elderly.