Cardiovascular Aging

Summaries of Ten Seminal Papers

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Experimental studies of physical fitness in relation to age

S. Robinson. *Arbeitsphysiologie. 1938*

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The effect of age on contractile protein ATPase activity and the velocity of shortening

N. R. Alpert and others. In: Tanz RD, Kavaler F, Roberts J, eds. *Factors Influencing Myocardial Contractility.* New York, NY: Academic Press, Inc; 1967

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Reduction in maximal oxygen uptake with age

I. Astrand and others. *J Appl Physiol.* 1973

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Diminished inotropic response of aged myocardium to catecholamines

E. G. Lakatta and others. *Circ Res.* 1975

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Decrease in the rate of RNA and protein synthesis and degradation in the myocardium under long-term compensatory hyperfunction and on aging

F. Z. Meerson and others. *J Mol Cell Cardiol.* 1978

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S. Port and others. *N Engl J Med. 1980*

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Role of aortic input impedance in the decreased cardiovascular response to exercise with aging in dogs

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Intracellular calcium transients and developed tension in rat heart muscle. A mechanism for the negative interval–strength relationship

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Age-associated changes in beta-adrenergic modulation on rat cardiac excitation–contraction coupling

R. P. Xiao and others. *J Clin Invest.* 1994

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J. L. Fleg and others. *J Appl Physiol.* 1995

Selection of seminal papers by **E. G. Lakatta, MD**
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Highlights of the years by
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Experimental studies of physical fitness in relation to age

S. Robinson

Arbeitsphysiologie. 1938;10:251-323

Although it was well recognized that older individuals have reduced exercise tolerance, this exhaustive work from the Harvard Fatigue Laboratory quantitatively sorted out the relative contributions of the cardiac, pulmonary, and hematological systems. Nestled amidst the pages of a German physiology journal, this 70-page tour de force (in English) actually makes for an interesting read on a rainy Sunday. Much of what we practice and preach today regarding exercise performance is rooted in this extensive report of physiological variables, recorded at rest and during treadmill exercise. The strengths of this work are the age range of the participants (6 to 91 years) and the completeness of the data collection.

Ninety-three males, who did not engage in athletics regularly, were subjected to measurements of heart rate (HR), blood pressure, lung parameters by spirometry, arterial blood gas, venous lactic acid, and oxygen utilization at rest and during two levels of exertion—minimal and exhaustive. For illustrative purposes, the subjects were separated into 12 age-groups including middle-class boys, "inmates of an orphanage," preparatory school and college students, and Harvard faculty.

At rest, HR did not change with age, although increasing age was related to decreased HR variability. Basal HR was positively correlated with the maximal HR achieved during exertion. Resting metabolic rate, measured as oxygen uptake per body surface area, declined precipitously with age until age 30, leveled off, and declined again after age 60. Age did not influence resting alveolar Po_2 and PCo_2, but lung vital capacity is decreased with age.

As predicted, maximal work and oxygen consumption decreased with increasing age. Peak exercise HR was also blunted with age as was the slope of HR decline in recovery. Despite the decrease in cardioacceleration, older men were more efficient at extracting oxygen as confirmed by increased blood lactic acid levels. Older men also had more efficient alveolar ventilation during exercise compared with the youngsters. This adaptation, coupled with an increased respiratory quotient (a surrogate measure of carbohydrate utilization), leads to a more economical energy transfer during exercise. In contrast to this increased efficiency in older men, younger boys, who seem unbothered by spurts of activity, had lower lactic acid levels, implying a decreased capacity to deliver oxygen to tissues despite higher HRs during activity.

Robinson also noted an age-related difference in the adaptive nature of the cardiovascular system during stress. Whereas rapid adjustments of respiratory rate, oxygen intake, and directional shunting of blood occur in the young, these stress-induced adaptations take longer in older adults. This implies a greater reliance on the autonomic nervous system during moderate work in younger boys.

In summary, this work addresses the heart of the matter of the limited exercise tolerance in the elderly by identifying the central role of age-related physiological changes in the cardiovascular system. In 1870, Adolph Fick noted that oxygen consumption is directly related to the flow of blood (HR × stroke volume) and indirectly to oxygen extraction by the tissues. Robinson's work provides evidence that the diminished maximal HR with age is paramount in reducing oxygen consumption during exercise, a seminal observation that has stood the test of time.

1938

George and Ladislav Biro invent the ball-point pen; Hitler marches into Austria proclaiming political and geographical union with Germany; and Orson Wells broadcasts his adaptation of H. G. Wells's "War of the Worlds," creating a nationwide panic as listeners believe that aliens have landed in New Jersey

The effect of age on contractile protein ATPase activity and the velocity of shortening

N. R. Alpert, H. H. Gale, N. Taylor. In: Tanz RD, Kavaler F, Roberts J, eds.

Factors Influencing Myocardial Contractility. New York, NY: Academic Press, Inc; 1967:127-133

While age-associated changes in physiology were being studied in a variety of species, Albert et al set out to explore both possible biochemical and mechanical alterations at the myocyte level. The goal of these experiments was to investigate the relationship between a biochemical property (ATPase activity) and the mechanics of contraction. Since prior work had suggested an age-related diminution in ATPase activity, myocytes of rats of various ages were used to gain insight into the influence of this biochemical alteration on myocardial contraction. Thus, although the aging process was actually exploited as an experimental condition, seminal observations were revealed about myocyte aging: a prolonged contraction duration with preserved contractile force.

The experimental design used by Alpert and coworkers was relatively simple: they measured ATPase activity in myofibrils isolated from hearts of Simonsen rats of various ages (100 to 1000 days old) in response to increasing concentrations of calcium. To correlate this biochemical measurement to the mechanical properties of the myocytes, force velocity, length tension, series and parallel elasticity, and time to peak tension and half relaxation were recorded in cells of the same hearts.

Myofibrillar ATPase activity increased with escalating calcium levels regardless myocyte age. The dependence of ATPase activity on calcium exists even when myofibrils are extracted with glycerol, implying a relationship that is independent of a membrane property. Although age did not affect the relationship between myofibrillar ATPase activity and calcium concentration, the overall ATPase activity was decreased by 14% in myocytes from the old compared with the young hearts.

The influence of age on the mechanical properties of the myocytes was surprising in these experiments. Age did not affect the amplitude of the contraction or the length–tension relationship, but interestingly, the shortening velocity was decreased as a function of increasing rat age. This relationship held true regardless of the initial load. Thus, although the contractile force in older cells is as intense as in younger myocytes, the contraction develops more slowly and lasts longer in older cells. Moreover, the correlation between the diminished myofibrillar ATPase activity and a prolonged contraction duration suggests a possible biochemical explanation for this mechanical alteration.

Given the experimental design, definitive conclusions regarding a cause-effect relationship between ATPase activity and prolonged myocardial contraction in aging could not be drawn. On a cellular level, the observation of a powerful, but slower, contraction in older myocytes raises the possible role of an age-related alteration in intracellular calcium cycling, perhaps by the sarcoplasmic reticulum, in these mechanical changes. The unchanged amplitude of contractile force in aged myocytes suggests either an alteration in calcium timing and/or superimposed stiffness. Regardless of the mechanism, this important characteristic of cardiovascular aging, prolonged contraction and therefore relaxation, is consistent across a multitude of species and has important clinical implications. A delay in early diastolic left ventricular filling may lead to symptoms of dyspnea, angina, and lightheadedness when an older individual is faced with a tachycardic stress.

1967

Christian Barnard performs
the world's first successful heart transplant,
but the patient dies 18 days later;
Jerome Friedman, Henry Kendall, and Richard
Taylor discover that protons and neutrons are
composed of even smaller particles called quarks;
and a right-wing military coup deposes
King Constantine II of Greece

Reduction in maximal oxygen uptake with age

I. Astrand, P. O. Astrand, I. Hallback, A. Kilbom

J Appl Physiol. 1973;35:649-654

One of the greatest challenges in the field of aging research is to distinguish those physiologic changes that are due to normal aging from those changes influenced by lifestyle, disease, diet, exercise, and environmental factors. Another potential confounder of gerontological studies is the birth-cohort effect. Cross-sectional studies, which consist of a single measurement in time of individuals of various ages, are particularly subject to these shortcomings. Yet, because they are simple, economical, and efficient to perform, cross-sectional studies provide the majority of our early understanding of physiological changes associated with aging. Longitudinally collected data, obtained by repeated measurements of the same variables in the same subjects over time, can overcome some of the limitations of cross-sectional data.

In an effort to alleviate concern that prior studies reporting an age-related decline in oxygen consumption with exercise were tainted by their cross-sectional design, two Swedish exercise physiologists, the Astrands, reported longitudinal changes in exercise parameters by collecting data from Swedish gym teachers who had been studied 21 years earlier. Forty-four female and 42 male physical education students initially performed submaximal and maximal exercise on a bicycle ergometer and treadmill in 1949. In 1970, the investigators tracked down 35 and 31 of the original women and men, respectively, to undergo similar exercise testing. It is noteworthy that since subjects were involved in teaching physical fitness, most exercised regularly over the 20 years and remained svelte.

With each subject serving as his or her own control, longitudinal changes in cardiopulmonary parameters were described. Although some technical differences exist between the 1949 and 1970 data collection, the novelty of these longitudinal data persists. In 1949, the average age of the female and male subjects was 22 and 26 years, respectively. Over the 21 years, women gained about 2.5 kilograms, whereas men lost about the same amount. Regarding lung function, vital capacity did not change over time, but residual volume decreased suggesting a longitudinal increase in total lung capacity. Consistent with cross-sectional data, maximal oxygen uptake, measured by a Douglas bag, decreased over time by 22% in women and 20% in men. This decrease was not influenced by changes in weight. Also demonstrated in numerous cross-sectional studies, an age-associated decrease in cardioacceleration during exercise was confirmed by these longitudinal data.

In this group of health-conscious athletes, a decrease in maximum oxygen consumption underscores a true age-associated physiological change rather than a decrease in overall activity over time. Although it is possible to raise oxygen consumption by a brief exercise program, it is unlikely that such consistent findings could be explained by a quick "buffing up" period just before the 1970 testing. When considering the candidate changes that may impact the decrease in oxygen consumption, prior cross-sectional studies pointed to the decrease in maximal heart rate with exercise. However, in this longitudinal study, the discrepancy between a 7% decrease in cardioacceleration and a 20% decrease in oxygen consumption raises the possibility of an additional age-associated diminution in stroke volume and/or tissue oxygen extraction. An increase in lactic acid content in 1970 may suggest the latter.

1973

Chile's Marxist president,
Salvadore Allende, is overthrown in a
military coup by General Augusto Pinochet;
Spanish painter and sculptor
Pablo Picasso dies, aged 92;
and a cease-fire is signed ending the involvement
of American ground troops in the Vietnam war

Diminished inotropic response of aged myocardium to catecholamines

E. G. Lakatta, G. Gerstenblith, C. S. Angell, N. W. Shock, M. L. Weisfeldt

Circ Res. 1975;36:262-269

Independent laboratory work and clinical observations in humans and animals consistently report a decrease in the cardiovascular responsiveness to stress with increasing age. Specifically, diminished maximal heart rate, decreased peripheral vasodilation, and dampened myocardial contractility to stress raised concern of altered catecholamine production and/or response. Similar physiologic changes in younger subjects after β-blockade further supported an adrenergically-mediated alteration. Lakatta et al address possible mechanisms underlying the age-related decrease in cardiovascular performance to β-adrenergic stimulation (βAS) in this elegant series of experiments on isolated rat heart muscle. By using isolated myocardium, the investigators established that the blunted inotropic stress response with age was due to "intrinsic" changes in the myocytes rather than to a defect in the elaboration of catecholamines.

Left ventricular trabeculae carnae muscle preparations were isolated from young adult (6 months old), middle-aged (12 months old), and old (25 months old) Wistar rats. Contractile parameters of the heart muscles were measured at baseline and in response to increasing concentrations of norepinephrine (NE). Similar measurements were made at differing calcium concentrations to tease out the role of calcium availability in catecholamine response.

Basal resting tension, active tension (AT), and maximal rate of tension development (dT/dt) were unchanged with age. However, as previously described in vitro *(see Alpert et al summary)* and in vivo, contraction duration in the oldest muscle was 17% and 19% longer than in the muscle of young adult and middle-aged rats, respectively ($P<0.001$).

Increased concentrations of NE lead to increased dT/dt, AT, and contraction duration shortening. Despite the consistency of these general responses to βAS, significant age-dependent differences were seen. Specifically, dT/dt to the highest dose of NE was twofold greater in the youngest compared with the oldest muscle ($P<0.001$). Whereas AT increased to NE in young and middle-aged muscle, it remained constant in the oldest tissue. Similarly, contraction duration shortening to the highest concentrations of NE was less robust in the oldest myocardium. By demonstrating similar age effects with NE and isoproterenol (which has higher receptor affinity and is negligibly taken up by storage sites), the investigators demonstrate that the diminished inotropic response with increasing age is unlikely related to altered β-adrenergic receptor affinity or storage site uptake.

In contrast to the blunted response to catecholamines in aged myocardium, there is no age difference in the increase in dT/dt or AT to increasing concentrations of calcium. This finding supports that the aged myofilament apparatus and its contractile ability are intact when calcium is abundant. The catecholamine-induced increase in contractile force and twitch duration shortening are governed by calcium presence at the contractile protein site. Thus, the blunted inotropic response to βAS may be explained by an inability of catecholamines to liberate intracellular calcium to the degree needed for contraction.

By performing these experiments on three age-groups, thereby providing dose-response curves, the authors confirm that the inotropic response to βAS is blunted with age. Moreover, they provide evidence supporting an alteration intrinsic to the aging myoctye that may be due to calcium cycling.

1975

Manuel Orantes and Chris Evert win the US open tennis championships (for men and women, respectively); Pol Pot and the Khmer Rouge take over Cambodia; and John W. Comforth (Australia) and Vladimir Prelog (Switzerland) are awarded chemistry Nobel Prize for research on structure of antibiotics and cholesterol

Decrease in the rate of RNA and protein synthesis and degradation in the myocardium under long-term compensatory hyperfunction and on aging

F. Z. Meerson, M. P. Javich, M. I. Lerman

J Mol Cell Cardiol. 1978;10:145-159

In the mid 1950s, Sir W. Pickering, in referring to the similarities between long-standing hypertension and aging, likened aging to "muted hypertension" and hypertension to "accelerated aging." This statement is supported by both clinical and experimental observations, including cardiac hypertrophy, a prolonged rate of contraction, normal baseline contractile function, in both circumstances. Animal models of hypertension, such as aortic banding, were established to gain further insight into the possible similarities between these two conditions. In this series of experiments, Meerson and colleagues compare and contrast the myocardial effects of hypertension and aging at the molecular level.

To address their hypothesis that aging and hypertension manifest as alterations in the myocardial balance of protein synthesis and degradation, the investigators measured RNA concentration, the rate of RNA and protein synthesis, and efficiency of protein translation in myocardium from three groups of rats. One experimental group of rats were aged (23 months old) while the hypertensive group consisted of 11-month-old rats that had undergone 6 months of abdominal aortic banding. Three- to 4-month-old nonhypertensive rats served as the reference group.

The absolute mass of the hearts of the hypertensive rats increased by 31% in comparison with control adult rats, with a significant increase in the heart weight–to–body weight ratio. The hearts of older rats also increased in weight, but the heart weight–to–body weight ratio was similar to that of younger control rats. A 20% decline in myocardial RNA concentration was noted in both aged and hypertensive myocardium compared with younger animals. While the rate of RNA synthesis was also depressed in aged and hypertensive myocardium, the latter was decreased by an additional 25% more than the former. Diminished transcriptional levels caused by a fall in RNA degradation led to a decreased ribosome content in the myocytes and thus the decreased RNA concentration. In vitro and in vivo evidence is provided that myocardial protein synthesis and degradation rates are similarly depressed in hypertension and aging. A reduction in the numbers of ribosomes and an altered ability to synthesize proteins are thought to contribute to the 46% decrease in protein synthesis seen in both aged and hypertensive myocardium. Deficiencies in transfer RNA (tRNA) may decrease the translational rates and also contribute to the decrease in protein synthesis. Thus, a loss in capacity for RNA and protein turnover and renewal of ribosomes leads to an accumulation of "defective" macromolecules in the myocytes.

The authors conclude that, because of similar changes in the myocyte at the molecular level including a decrease in synthesis and degradation of RNA and protein, hypertension serves as a model for cardiovascular aging. While cardiac hypertrophy due to aging and hypertension share some similarities at the molecular level, differences in these two conditions also exist. Aging is associated with hypertrophy of the right as well as the left ventricle, and the magnitude of this hypertrophy is far less than that which occurs in hypertensive models. In both cases, hypertrophy appears to be related to the increased afterload of stiffened vasculature. While the cumulative pathway of increased cell length and loading is similar in the two conditions, the commonality may lie upstream, as in a common messenger such as calcium (see Lakatta, *Circulation,* 1987;75(suppl I):I69, for review).

1978

Louise Brown, the first test-tube baby,
is born at Oldham Hospital in London;
Italian prime minister Aldo Moro is kidnapped
and killed by left-wing terrorists;
and Sony introduces the Walkman

Effect of age on the response of the left ventricular ejection fraction to exercise

S. Port, F. R. Cobb, R. E. Coleman, R. H. Jones

N Engl J Med. 1980;303:1133-1137

A dilemma developed in how to apply the building body of evidence from laboratory studies regarding age-related cardiovascular changes to the clinical arena. Two obstacles prevented extrapolation from in vitro data to humans: the simplicity of the model and the jargon of contractility. Animal models consistently demonstrated prolonged baseline myocardial contractility and a blunted inotropic response to β-adrenergic stimulation with increasing aging. Moving from the test tube to the organism level is complicated by the inseparable interactions between preload, contractility, afterload, and autonomic control. Moreover, when describing myocardial function clinically, ejection fraction (EF) seems to serve as the universal language. All prior aging studies reported measures of contractility such as stroke volume, developed tension, or active tension. Although EF is not truly a measure of contractility, it is the currency of clinical and therapeutic decisionmaking. The time had come to bridge the aging rat data to the clinical realm. Implementing a new technology, radionuclide angiocardiography, Port et al set out to establish whether resting EF or peak exercise EF changed with age.

The subjects consisted of 77 healthy volunteers (31 women and 46 men), screened for known cardiovascular, pulmonary, renal disease, as well as hyperlipidemia, excessive smoking, diabetes, and hypertension. The participants, who ranged in age from 20 to 95 years, underwent upright bicycle ergometry, while EF was determined by first-pass radionuclide angiocardiography. This technique allows for the assessment of regional wall motion abnormalities (RWMAs).

Consistent with the results of Robinson 42 years before *(see summary),* resting heart rate (HR) did not change with age, but systolic blood pressure (BP) increased with age. Despite an increase in systolic BP, mean BP was unaltered with age, confirming another hallmark of cardiovascular aging—increased central arterial stiffness. No relationship between age and resting EF (mean±SD = 0.64±0.07) or left ventricular end-diastolic volume index (LVEDVI) was seen. Moreover, no RWMAs were detected at rest.

At peak cardiac workload, EF decreased with increasing age. While only 1 of the 48 subjects under age 60 had a peak EF<0.60, 13 of 29 subjects over age 60 had a peak EF<0.60. This finding supports an age-associated reduction in contractile reserve. An age-related change in LVEDVI did not account for the EF reduction. It is tempting to speculate that reduced HR accounts for declined EF. However, using linear regression, the authors conclude that failure to augment HR alone did not fully explain the dampened EF.

This study also gave birth to a realization of the magnitude of "silent" ischemia in the elderly. Although no subject experienced anginal symptoms during exercise, positive electrocardiographic changes consistent with ischemia were seen in 2 older subjects (66 and 74 years old). While no exercise-induced RWMAs were seen in subjects under age 50, they increased with age, such that 44% of subjects in their 8th through 10th decade developed RWMAs during exercise. This finding was reproduced by Fleg et al who report 30% of myocardial infarctions are "silent" in the elderly (*Circulation,* 1990,81:423).

The authors conclude that while resting EF does not vary with age, EF at peak exercise is reduced with increasing age. They speculate that while structural and biochemical alterations may contribute to these changes, the impact of silent ischemia must not be overlooked.

1980

John Lennon, former member of the "Beatles," is killed by Mark Chapman in New York; Archbishop Oscar Romero, a fierce critic of the political extremists in El Salvador, is shot and killed; and Mount St Helens blows its top in Washington State

Role of aortic input impedance in the decreased cardiovascular response to exercise with aging in dogs

F. C. Yin, M. L. Weisfeldt, W. R. Milnor

J Clin Invest. 1981;68:28-38

Around the same time Port and coworkers were pursuing the impact of age and myocardial contractile reserve on decreased exercise performance, Yin et al focused their attention on the possible contribution of increased afterload. Rather than the simplistic view that the vasculature acts in accordance to Ohm's Law, these investigators sorted out the relative impact of steady (resistance) and pulsatile (characteristic impedance [CI]) loads imposed by the vasculature on the ejecting left ventricle both at rest and during exercise. Additionally, they sought to understand the influence of age on catecholamines. Their hypotheses were that with aging (i) increased vascular stiffness contributes to the decreased cardiac response to exercise and (ii) a decreased inotropic and chronotropic response to β-adrenergic stimulation (βAS) contributes to the blunted exercise performance. The experimental model employed in this study was novel: young and old dogs that were chronically instrumented with a probe that simultaneously measures blood flow and pressure. Recordings were made at rest and during a treadmill exercise, before and after pharmacological β-adrenergic blockade.

At rest, no difference was found between the seven 2-year-old and seven 10-year-old beagles in heart rate (HR), stroke volume (SV), cardiac output aortic pressures, or impedance. In contrast, exercise elicited significant age-related differences in vascular and thus cardiac performance. A marked reduction in exercise tolerance was noted in old dogs, none of which completed the new trick of extreme exercise. At low levels of exercise, vascular resistance was decreased in both young and old dogs. Whereas this steady component of vascular impedance continued to fall during moderate and severe exercise in the young dogs, it remained constant during these higher exertional levels in the older dogs. Contributing more to the diminished SV attained by the older dogs during peak exercise, the pulsatile component of afterload, CI, increased by 20% during low levels of exercise and remained elevated during higher work levels. In contrast, CI dropped during exercise in the young dogs. Aortic acceleration, a measure influenced by both load and inotropy, remained constant throughout exercise, regardless of age. Therefore, increased load is implicated in the decreased inotropy at peak exercise levels in older dogs.

Catecholamines play an important role in the regulation of cardiovascular response to exercise by influencing inotropic, chronotropic, and vasodilatory response. Decreased responsiveness to βAS with aging plays an important role in the age-related changes in vascular load and inotropy during exercise. Blockade of β-adrenergic receptors with propranolol abolished the age-related differences in vascular loading during exertion. Specifically, CI increased during exercise in β-blocked younger dogs resulting in diminished SV.

In summary, an increase in pulsatile load during exercise appears to contribute to the diminished SV (and therefore cardiac output) achieved during exercise in older dogs. This component of afterload is largely influenced by changes in the size and structure of the proximal central vasculature. At higher levels of activity, decreased response to βAS also contributes to the increased vascular load and decreased exercise tolerance in older individuals.

1981

Egyptian president Anwar el-Sadat
is assassinated by Islamic extremists during
a military parade in Cairo;
Ronald Reagan and Pope John Paul II
survive assassination attempts;
and Prince Charles marries Lady Diana Spencer:
the wedding has a worldwide television
audience of over 700 million

Intracellular calcium transients and developed tension in rat heart muscle. A mechanism for the negative interval–strength relationship

C. H. Orchard, E. G. Lakatta

J Gen Physiol. 1985;86:637-651

One of the hallmarks of cardiovascular aging is prolonged myocyte contraction, which leads to delayed early diastolic filling. Speculation arose that a lengthened intracellular calcium (Ca^{2+}) transient could be responsible for this age-related change. In normal excitation-coupling, an initial depolarization causes Ca^{2+} influx through L-type sarcolemmal Ca^{2+} channels delivering Ca^{2+} to myofilaments for contraction. Calcium is then removed from the cytoplasm by sarcolemmal ATP-dependent Ca^{2+} pumps. These oscillations in intracellular Ca^{2+} currents require a certain amount of time for reconstitution. Given the complexity of Ca^{2+} cycling, there are numerous targets for possible age-associated alterations that may lead to a lengthened Ca^{2+} transient. This series of experiments by Orchard and Lakatta exploit the chemiluminescent jellyfish protein aequorin as a surrogate measure of cytoplasmic Ca^{2+} to explore the possible alterations in cycling that may prolong contraction.

The primary goal of this work was to establish the relationship between the intracellular Ca^{2+} transient and developed tension in response to varying rates of stimulation. A negative interval–strength relationship exists in rat myocardium such that increased stimulation frequency leads to decreased developed tension. The relationship between Ca^{2+} transients and developed muscle tension is explored. The experiments were performed on papillary muscles isolated from young adult (5 to 7 months old) and aged (24 months old) Wistar rats. Developed tension to electrode stimultion was measured by a tension transducer attached to the nonfixed end of the muscle. Injecting aequorin into superficial muscle cells and measuring the light signal with a photomultipier tube–quantitated myoplasmic Ca^{2+} concentrations. The contractile properties and intracellular Ca^{2+} transients were recorded to different stimulation frequencies and in various Ca^{2+} bath concentrations.

The aequorin light transient, which reflects intracellular Ca^{2+} level, was closely correlated with peak tension of the papillary muscles (r=0.89). Similar amplitudes of aequorin light transients were seen in myocardium from 6-month-old and 24-month-old rats. However, despite these comparable levels of total intracellular Ca^{2+} and twitch force in old and young myocardium, both the time-to-peak tension and the half-time relaxation of developed tension were delayed in aged myocytes. The authors speculate that this prolonged tension and slower rate of relaxation may be due to slower sequestration of calcium by the sarcoplasmic reticulum (SR).

Consistent with previous studies on rat myocardium, increased stimulation rate was associated with decreased Ca^{2+} transient and decreased developed tension. This finding was consistent in both age-groups. However, when performed in a bath of increased Ca^{2+} concentration, the contractile response to increased stimulation frequency of young muscle was no longer diminished. In contrast to the ability of the young myocardium to overcome this negative interval–strength relationship when performed in the presence of higher Ca^{2+} concentrations, aged myocardium continued to respond to increased stimulation frequency with decreased intracellular Ca^{2+} transient and developed tension. The investigators conclude that the negative interval–strength relationship may be due to an age-associated alteration in the time-dependent repriming of the SR with Ca^{2+}.

1985

Coca-Cola attempts to alter its 99-year-old formula to attract younger drinkers: the new Cola flops and they return to the original product; Mikhail Gorbachev becomes the Soviet leader and instigates a broad range of reforms; and British scientists report the appearance of an enormous hole in the ozone layer over Antarctica

Age-associated changes in beta-adrenergic modulation on rat cardiac excitation–contraction coupling

R. P. Xiao, H. A. Spurgeon, F. O'Connor, E. G. Lakatta

J Clin Invest. 1994;94:2051-2059

Age-associated decrease in cardiovascular responsiveness to β-adrenergic stimulation (βAS) is characterized by a decrease in heart rate (HR) augmentation, left ventricular dilatation, and a decrease in contractility during exercise. When stress-induced plasma catecholamines (epinephrine and norepinephrine [NE]) were found to be higher in older compared with younger adults, investigators turned their attention to possible postsynaptic mechanisms to explain the blunted stress response. Further evidence supporting an age-related postreceptor alteration is the diminished contractility and HR augmentation of aged myocardium to exogenous catecholamines. The report by Orchard and Lakatta *(see summary)* of an age-related change in myoplasmic Ca^{2+} transients in response to NE, prompted Xiao and colleagues to test several stages of the postreceptor cascade leading to contractility in an attempt to identify (a) specific age-related change(s). The authors assessed the relative contributions of the inward Ca^{2+} current (sarcolemmal) $I_{Ca^{2+}}$, the cytosolic Ca^{2+} transient, and the contractility of myocytes isolated from hearts of rats of three age-groups, 2, 6, and 24 months old. Calcium levels were measured using a fluorescent Ca^{2+} probe and $I_{Ca^{2+}}$ was quantified by the voltage clamp technique.

Myocytes from rat hearts from the various age-groups were first observed for baseline contractile performance. No age-associated difference was noted in the twitch amplitude or maximum shortening velocity despite a slightly increased diastolic length in the oldest cells. The Ca^{2+} transient during baseline contraction was also consistent across age-groups, however, the ratio of Ca^{2+} in diastole was higher in older cells.

Excitation-contraction (E-C) coupling is initiated by an initial membrane depolarization, which triggers the $I_{Ca^{2+}}$ through the sarcolemmal Ca^{2+} channels. The $I_{Ca^{2+}}$ triggers a Ca^{2+}-dependent Ca^{2+} release from the sarcoplasmic reticulum (SR), where it is recycled after contraction through a Ca^{2+}-dependent ATPase pump. No age-associated compromise in the intrinsic E-C mechanism was justified by the normal resting performance. After exposure to increasing concentrations of NE, the younger myocytes demonstrated increased twitch amplitude and velocity with an increased $I_{Ca^{2+}}$. In contrast, aged myocytes display a diminished contractile response (twitch amplitude and velocity) and decreased $I_{Ca^{2+}}$ to increasing concentrations of NE. The amplitude and maximal rate of rise of the Ca^{2+} transient are surrogate measures for the excitation-induced release of calcium from the SR. In addition to a decreased SR Ca^{2+} release, relaxation, which is governed by Ca^{2+} sequestration by the SR, is also prolonged. The authors postulate that altered recycling of Ca^{2+} may be related to decreased phosphorylation of SR phospholamban by βAS.

To ensure that the results of these experiments were not influenced by the small amount of α-adrenergic stimulation of the mixed agonist (NE), the studies were reperformed with the α-adrenergic blocker prazosin, and yielded similar results.

This elegant series of experiments shed light on the role of intracellular Ca^{2+} cycling in the diminished contractile response of age myocardium to catecholamine stimulation. The investigators provide evidence that an initial decrease in $I_{Ca^{2+}}$ contributes to the age-associated decrease in myoplasmic Ca^{2+} transient and thus contractility. Moreover, a delay in SR Ca^{2+} recycling may contribute to the delay in diastolic relaxation. These observations may help us to better understand the decreased response of the older heart to stress and, hence, where to target therapeutic interventions.

1994

Martina Navratilova plays her final singles tennis match after a peerless career;
Russian aircraft bomb the Chechen capital of Grozny; and Chandrika Kumaratungas' Peoples' Alliance party sweeps to power in the Sri Lankan general election

Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women

J. L. Fleg, F. O'Connor, G. Gerstenblith, L. C. Becker, J. Chulow, S. P. Schulman, E. G. Lakatta

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The effort to understand why older individuals have a decreased exercise capacity continues. To this point, it was accepted that with increasing age, heart rate (HR) augmentation and cardiac contractility are diminished. The new hot topics of debate in the 1990s were (i) were there specific gender differences in exercise? and (ii) did the Frank-Starling mechanism actually apply to humans?
Three unique spins to the exercise story underscore the significance of this work by Fleg et al for our understanding of the relationship between exercise and age. First, the application of a new technology, gated cardiac blood pool scans, provided insight into the changes in cardiac volumes at rest and during exercise. Previous correlation with cardiac catheterization validated this technique, which is now used for noninvasive assessment of cardiac performance during exercise. Second, the primary goal of the investigators was to understand gender differences in cardiac performance at rest and during exhaustive exercise. To this end, 79 female and 121 male healthy volunteers from the Baltimore Longitudinal Study of Aging (BLSA) were studied. Third, the subjects in this study were rigorously screened and excluded for any evidence of overt or occult cardiovascular disease. Exclusion criteria included any cardiovascular diagnoses or medications, an abnormal electrocardiogram, or a positive exercise stress test. Moreover, subjects over 40 had to confirm no evidence of coronary disease on an exercise thallium test.

Resting hemodynamics revealed a decrease in HR and an increase in systolic blood pressure (SBP) with increasing age in both genders. However, women had higher HR and lower SBP than men. A 46% increase in total peripheral vascular resistance (TPVR) and a 16% decrease in cardiac index (CI) was noted in women at rest, but not in men. On the other hand, resting cardiac volumes (end-diastolic and systolic volume index [EDVI and ESVI] and stroke volume index [SVI]) increased roughly 20% across the age span in men, but remained unchanged in females. Measures of cardiac pump function at rest, such as ejection fraction and myocardial contractility (SBP/ESVI), were not influenced by age in either gender, but were consistently higher in women.
As in prior studies, the exercise capacity of older men and women was diminished by 40%. At peak effort in both genders, an age-related decline in EF, HR, and CI, and an increase in SVI and TPVR compared with younger subjects were noted. The cardiovascular mechanisms used to attain peak performance, however, varied greatly according to gender. During exercise, the HR of women increased at a steeper rate than that of men. This may be compensatory for the smaller cardiac volumes seen in women. In contrast, men rely more heavily on the Frank-Starling mechanism to increase cardiac performance. Not only did men have higher cardiac volumes at rest, but during exertion, EDVI and ESVI remained higher than in women. To maintain the same SVI as younger subjects during exercise, older men, but not women, had a significantly elevated EDVI. As expected, ESVI increased during exercise in both genders, but was not influenced by age. Thus, the relationship between EDVI and SVI in older men during exertion is shifted upward and to the right compared with younger men and women.

In summary, cardiac reserve during exercise is blunted in both genders, but the specific hemodynamic strategies brought into play in women and men during exercise are unique. Men rely more heavily on the Frank-Starling mechanism to preserve SVI, whereas women depend on an increased heart rate. Consistent with the findings of Port et al *(see summary)* and despite rigorous screening, peak cardiac pump performance (EF, CI, and SBP/ESVI) declined with age, although SVI was not influenced by age.

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British trader Nick Leeson is arrested for his role in the collapse of Barings Bank PLC; The graves of Czar Nicholas and his family are found in St Petersburg; and poison gas is released in the Tokyo subway, killing 12 and injuring thousands more: the attack is linked to the Aum Shinrikyo religious sect