1984 YEAR BOOK OF CARDIOLOGY

HARVEY / KIRKENDALL
KIRKLIN / NADAS
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The YEAR BOOK of

Cardiology®

1984

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The editor for this book was Jane Toomey, and the production manager was H. E. Nielsen.

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The material covered in this volume represents literature reviewed up to December 1983.

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Acta Medica Scandinavica
American Heart Journal
American Journal of Cardiology
American Journal of Clinical Nutrition
American Journal of Epidemiology
American Journal of Medicine
American Journal of Physiology
American Journal of Roentgenology
Annals of Emergency Medicine
Annals of Internal Medicine
Annals of Rheumatic Diseases
Annals of Surgery
Annals of Thoracic Surgery
Archives of Internal Medicine
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Hypertension
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Journal of the American Academy of Dermatology
Journal of the American College of Cardiology
Journal of the American Medical Association
Journal of Applied Physiology: Respiratory, Environmental, and Exercise Physiology
Journal of Cardiovascular Surgery
Journal of Clinical Investigation
Journal of Epidemiology and Community Health
Journal of Occupational Medicine
Journal of Pediatrics
Journal of Pharmacology and Experimental Therapeutics
Journal of the Royal College of General Practitioners
Journal of Thoracic and Cardiovascular Surgery
Lancet
Mayo Clinic Proceedings
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New England Journal of Medicine
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Pfluger's Archiv. European Journal of Physiology
Postgraduate Medical Journal
Presse Medicale
Radiology
Science
Stroke
Thorax
Yale Journal of Biology and Medicine

1. Normal and Altered Cardiovascular Function

1–1 **Interaction Between Adenosine and Inotropic Interventions in Guinea Pig Atria.** Adenosine has been found to attenuate catecholamine-induced enhancement of the contractile state in cardiac muscle, independent of its negative inotropic effect on such muscle. James G. Dobson, Jr. (Univ. of Massachusetts), with the technical assistance of Lynne G. Shea, examined the effects of adenosine on interventions that enhance force development and contractility in isolated, isometrically contracting guinea pig atria. The measures included an increase in muscle length (preload), paired electric stimulation to produce postextrasystolic potentiation, an increase in contraction frequency, and catecholaminergic stimulation in both potassium-depolarized and nondepolarized atrial muscle.

Adenosine did not influence the contractile variables that were enhanced by an increase in preload or by paired electric stimulation, but it reduced the increases in contractile variables produced by isoproterenol. These effects of adenosine were inhibited by theophylline, an adenosine antagonist, but not by atropine or propranolol.

Adenosine can attenuate the increase in contractility produced by catecholamine stimulation without causing a direct negative inotropic response. The effects appear to be independent of catecholamines. A reduction in the catecholamine-induced rise in myocardial cyclic adenosine monophosphate may be involved, with subsequent modulation of cellular Ca^{2+} concentrations.

▶ [The relationship of the adenosine modulation of catecholamine responses to physiologic events has yet to be determined. Nevertheless, the mechanisms and effects of these complex metabolic interactions require further consideration.—E.H.S.] ◀

1–2 **Actions of Adenosine and Isoproterenol on Isolated Mammalian Ventricular Myocytes.** Adenosine specifically antagonizes the inotropic, and some of the electrophysiologic and metabolic, effects of catecholamines on ventricular myocardium, possibly partly through inhibiting the release of norepinephrine from adrenergic nerve endings. Luiz Belardinelli and Gerrit Isenberg (Univ. of Saarland) assessed the postjunctional antagonistic action of adenosine on the electrophysiologic and contractile effects of isoproterenol in isolated ventricular myocytes from adult guinea pig and bovine hearts. Both

(1–1) Am. J. Physiol. 245:H475–H480, September 1983.
(1–2) Circ. Res. 53:287–297, September 1983.

the perfusion and the chunk methods were used. Intracellular stimulation of relaxed myocytes led to action potentials with full plateaus and contractions. Adenosine at concentrations up to 0.2 mM did not significantly affect the action potential or basal contractility, but antagonized the stimulatory effects of isoproterenol. Isoproterenol prolongated the action potentials and markedly increased the extent of myocyte sarcomere shortening. These effects were inhibited in the presence of adenosine. The amplitude of the afterdepolarizations sometimes observed with isoproterenol was reduced by adenosine, and the resultant sustained rhythmic activity was abolished.

Isolated ventricular myocytes respond to isoproterenol, and adenosine effectively antagonizes its stimulatory actions while not directly affecting the myocytes. The findings in isolated myocytes in this study are consistent with those reported for multicellular ventricular preparations. The concentrations of adenosine needed to attenuate the effects of isoproterenol (5 to 50 μM) are in the range of the concentrations released by cardiac cells when oxygen availability is limited, demands are increased, or both. Endogenously released adenosine may modulate the electrophysiologic and contractile effects of exogenous catecholamines, increased sympathetic drive, or both under these conditions.

1–3 **Effects of Calcium Channel Blockers on Isolated Carotid Baroreceptors and Baroreflex.** The differential effects of calcium antagonists observed clinically could be due to mechanisms other than antagonism of the slow inward calcium current in cardiac and vascular muscle, such as effects on cardiovascular reflexes. Cheryl M. Heesch, Brian M. Miller, Marc D. Thames, and Francois M. Abboud (Univ. of Iowa) examined the effects of organic calcium antagonists on isolated carotid sinus baroreceptors and the baroreflex in dogs. The left carotid sinus region was vascularly isolated and filled with oxygenated physiologic salt solution, and steady state multiunit activity was recorded from the carotid sinus nerve at sinus pressures of 50 to 200 mm Hg as the region was bathed with nifedipine (10 μg/ml) or verapamil (5 μg/ml).

Nifedipine increased the sensitivity of the carotid sinus baroreceptors, whereas verapamil decreased it. Studies with bilateral carotid sinus isolation, in which the carotid sinus nerves were intact, indicated that nifedipine enhanced and verapamil attenuated the carotid baroreflex control of renal sympathetic nerve activity. Pressure-volume curves indicated that effects on smooth muscle did not account for the opposed effects of the two drugs. Omission of calcium ion from the physiologic solution led to increased carotid sinus nerve activity, an effect blocked by verapamil but not by nifedipine. Verapamil only inhibited veratrine-induced, sodium-dependent excitation of carotid baroreceptors.

(1–3) Am. J. Physiol. 245:H653–H661, October 1983.

The findings indicate that the excitatory effects of nifedipine on the carotid sinus baroreceptors are dependent on Ca^{2+} mechanisms, whereas the inhibitory effects of verapamil may be related chiefly to interference with the inward Na^{+} current. Direct evidence of the effects of Ca^{2+} channel blockers on ionic currents in baroreceptors would be helpful. It is clear, however, that nifedipine and verapamil have strikingly different effects on the baroreceptors, though both are classified as calcium antagonists.

▶ [These findings are interesting in that they suggest that the calcium blockers may exert their effects not only on vessels but on the reflex mechanisms that are generated by the carotid baroreceptors and baroreflexes. The significance of these findings warrants further investigation.—E.H.S.] ◀

1–4 **Dependence of Unloaded Shortening Velocity on Ca^{2+}, Calmodulin, and Duration of Contraction in "Chemically Skinned" Smooth Muscle.** Isometric force in "chemically skinned" smooth muscle depends on the Ca^{2+} and calmodulin concentrations, in accord with the proposal that the force level is related to myosin phosphorylation, but studies of living smooth muscle have indicated that both shortening velocity and myosin phosphorylation decrease with contraction duration. Richard J. Paul, Glenn Doerman, Claudia Zeugner, and J. Caspar Rüegg measured unloaded shortening velocity, a variable associated with the rate of cross-bridge cycling, in chemically skinned guinea pig taeniae coli and hog carotid artery. Shortening velocity was measured by rapidly imposing large length steps on the muscle and determining the time under unloaded conditions from isometric myograms.

Shortening velocity was similar to the V_{max} from Hill force-velocity relations reported for both living and skinned taeniae coli. For carotid artery, it was at least as great as that reported for living muscle. Shortening velocity showed qualitatively similar behaviors in both preparations. It was dependent strongly on temperature, and on both the Ca^{2+} and the calmodulin concentrations. Shortening velocity could be increased by adding Ca^{2+}, calmodulin, or both when isometric force was maximized. Maximization of myosin phosphorylation with adenosine triphosphatase-γS did not increase the shortening velocity beyond the maximum obtained with Ca^{2+} and calmodulin. The development of shortening velocity on exposure to high-Ca^{2+} solution preceded isometric force development. The steady state value was slightly below the maximum shortening velocity.

Although isometric force and shortening velocity are both dependent on Ca^{2+} and calmodulin in skinned smooth muscle, the dependencies are not identical, and the differences may explain the decline in shortening velocity associated with maintained isometric force in living smooth muscle. Smooth muscle seems able to "shift gears,"

(1–4) Circ. Res. 53:342–351, September 1983.

with reductions in both shortening velocity and energy utilization, while constant force is maintained.

▶ [It is interesting that both smooth muscle and cardiac muscle are dependent on levels of external calcium in the bath. If the number of forced generating bridges between actin and myosin were to be the only variable, the shortening velocity should be independent of calcium. Thus, this change in velocity with calcium remains unexplained in both tissues. Moreover, it is interesting that the same mechanical descriptions exist for both muscles even though the sarcomeric structure is absent in smooth muscle.—E.H.S.] ◀

1–5 **Distribution of Myosin Isozymes Within Single Cardiac Cells: Immunohistochemical Study.** Jane-Lyse Samuel, Lydie Rappaport, Jean-Jacques Mercadier, Anne-Marie Lompre, Saverio Sartore, Chiara Triban, Stefano Schiaffino, and Ketty Schwartz used affinity-purified antibodies reacting with the heavy chains of the major myosin isozymes of adult rat heart, V_1 and V_3, to localize isozymes in single myocytes in the hearts of adult control and hypophysectomized rats and 3-week-old rats and in cultured cardiac cells. Double immunolabeling of the same cells was carried out to demonstrate V_1 myosins with rhodamine and V_3 myosins with fluorescein. In the young rats, all cells were stained with anti-V_1 and almost none with anti-V_3 myosin. In hypophysectomized adults, all cells were stained with anti-V_3 and none with anti-V_1. A mixed pattern was found in adult controls, in which half the cells reacted with anti-V_1, 10% with anti-V_3, and 40% with both. Similar dual reactivity was evident in cultured cells. The distributions of the V_1 and V_3 reactivities were homogeneous throughout the cell and absolutely superimposable.

Myocytes from the adult rat myocardium are heterogeneous with regard to their isomyosin content. Two isomyosins can coexist and be equally distributed in the same cardiac cell. This approach may hold promise for elucidating the regulation of cardiac contraction at the filament level.

▶ [It is now a well-recognized fact that myosin exists in terms of three isozymes created by two distinct types of heavy chains, α and β, with V_1 being a homodimer of αα, V_3 being a homodimer of ββ, and V_2 being an α-β heterodimer (Hoh, J. H., et al.: *J. Mol. Cell. Cardiol.* 10:1053–1076, 1978, and Chizzonite et al.: *J. Biol. Chem.* 257:2056–2065, 1982). Velocity of muscle shortening has been directly correlated with the resultant ATPase activity of these various isozymes, with V_1 being the fastest and V_3 being the slowest (Barany, M.: *J. Gen. Physiol.:* 50:197–218, 1967, and Ebrecht, G. H., et al.: *Basic Res. Cardiol.* 77:220–234, 1982). At least in animals with systolic overloads, a change from V_1 to V_3 isozymes has been observed which correlates with the decrease in speed of contraction that is seen mechanically (Lompré, A. M., et al.: *Nature* 282:105–107, 1979). The present study shows that more than one isozyme may be present within an individual cell and this heterogeneity may strongly effect mechanical events in the activated cell.—E.H.S.] ◀

1–6 **Comparative Studies of Atrial and Ventricular Myosin From Normal, Thyrotoxic, and Thyroidectomized Rabbits.** Myocardial contractility and myosin adenosine triphosphatase (ATPase) ac-

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(1–5) Circ. Res. 52:200–209, February 1983.
(1–6) Ibid., pp. 131–136.