

ANTIARRHYTHMIC AGENTS

I. CARDIAC ELECTROPHYSIOLOGY

A. Resting membrane potential determined by ion gradients and membrane permeability

1. -80 to -90 mV in most cardiac cells
2. ionic gradients maintained by active transport (Na-K pump)
3. $[K]_i = 150 \text{ mM}$; $[K]_o = 4 \text{ mM}$; $[Na]_o = 140 \text{ mM}$; $[Na]_i = 30 \text{ mM}$ (typical values for ion gradients)
4. Nernst equation for an ion, X, $E = RT/F \ln(X_o/X_i)$ --- $E_K = -97 \text{ mV}$ and $E_{Na} = +40 \text{ mV}$ (E = equilibrium potential, R = gas constant and F = Faraday constant); equation can be rewritten as $E = 60 \log(X_o/X_i)$ for physiological temperature (subscripts refer to inside, outside concs.)
5. E_m approaches E_K because resting membrane is highly permeable to K^+ ions; there is a small influence of the Na gradient ($P_{Na}/P_K = .01$)
6. RMP lower in S-A and A-V node reflecting relatively high P_{Na}/P_K ratio in these specialized tissues

B. Action potentials

1. When the cardiac membrane is excited by an appropriate stimulus, what occurs is a complex sequence of membrane voltage changes called an action potential
2. Phases of Purkinje fiber action potential (see Fig.)
 - a. Phase 0 = rapid depolarization and reversal of transmembrane potential (overshoot)
 - b. Phase 1 = rapid repolarization to plateau level of voltage
 - c. Phase 2 = action potential plateau
 - d. Phase 3 = rapid repolarization to resting (diastolic) level of transmembrane voltage
 - e. Phase 4 = diastolic potential
3. Other action potential waveforms (Fig.)
 - a. Sinus and A-V nodal: slowly rising phase 0 and no phase 1
 - b. Some cell types have stable phase 4 (diastolic) potential (ventricle, atrial), whereas others have spontaneous diastolic depolarization
4. Determinants of automaticity in spontaneously-firing fibers (e.g. Purkinje, nodal)
 - a. maximal diastolic potential (more neg. implies slower rate)
 - b. slope of phase 4 depolarization (steeper means faster)
 - c. action potential threshold (more neg. means faster)
 - d. pacemaker cells (normally S-A node) have lowest MDP and steepest phase 4 slope; less automatic cells are "latent pacemakers"
5. Ion fluxes associated with Purkinje AP
 - a. phase 0 ---Rapid inward movement of Na^+ through voltage-dependent, selective Na channels
 - b. phase 1 ---inactivation of I_{Na} and turn-on of transient outward K^+ current
 - c. phase 2 ---slow Ca^{++} current, I_{si} (sustained); small non-inactivating component

of I_{Na} ?

- d. phase 3 ---turn on of delayed K^+ ion current plus gradual inactivation of I_{si}
- e. phase 4 ---complex: classically, deactivation of I_k in presence of inward background (Na, Ca) leak current.

C. Fast Response and Slow Response (see Fig.)

- 1. Fast response: phase 0 depolarization due to fast I_{Na} ; rapid upstroke velocity; normal for atrial, ventricular and Purkinje fiber action potential
- 2. Slow response phase 0 due to slow inward current; very slow upstroke and propagation velocity; normal for S-A node and A-V node; abnormal in ventricle (demonstrable in artificial condition -- K^+ depolarization plus catecholamine)

D. Effective refractory period of action potential

- 1. Minimum period between two propagating action potentials
- 2. In fast response fibers, this is approximately equal to action potential duration (APD)
- 3. In slow response fibers, this is considerably longer than APD

E. Membrane responsiveness curve (See Fig.)

- 1. Relationship between the maximal upstroke velocity of Phase 0 and E_m at the moment of depolarization
- 2. Indicates relation between membrane potential and the availability of the fast Na current
- 3. Significance: upstroke velocity is an important determinant of propagation velocity--under abnormal conditions of membrane depolarization upstroke velocity and hence conduction velocity will be reduced; moderate to high concentrations of quinidine and other antiarrhythmics shift curve to lower values (even with normal fibers)

II. MECHANISMS RESPONSIBLE FOR CARDIAC ARRHYTHMIAS

A. Definition: an abnormality of rate, regularity, or site of origin of the cardiac impulse or an alteration of the normal sequence of activation of atria and ventricles

B. Examples: sinus tachycardia or bradycardia; abnormal pacemaker site; partial or complete heart block (e.g., 2:1 A-V block)

C. Common atrial tachyarrhythmias

- 1. atrial fibrillation (350-800 beats/mm); atrial contraction ineffective; 130-170 beats/mm transmitted to ventricle (irregularly) prior to treatment
- 2. atrial flutter: regular rapid beating---250-300/min (effective contractions); 50% of impulses transmitted to ventricle
- 3. paroxysmal atrial tachycardia (ca. 200 beats per mm); all impulses transmitted; usually terminates spontaneously and can occur in the absence of underlying disease

D. Common ventricular arrhythmias

- 1. ventricular extrasystoles (premature beats): originate in ventricles; bizarre QRS, no P wave; premature interruption of dominant rhythm; possible cause--automaticity that arises in ectopic focus (likely to be within Purkinje system); often associated with acute phase of myocardial infarction or digitalis toxicity and may presage more serious dysrhythmias

2. ventricular tachycardia: 150-200 beats per mm; can produce circulatory impairment, congestive heart failure and severe hypotension

E. Abnormal automaticity

1. Depolarized atrial, ventricular, or Purkinje fibers (beyond -60 mV) will cause phase 4 depolarization and spontaneous firing; such cells could become abnormal pacemakers
2. Abnormal automaticity facilitated by catecholamines

F. Triggered activity

1. Definition: the generation of impulses by afterdepolarizations that reach threshold (this can also occur in cells that ordinarily are incapable of automatic activity)
 - a. early afterdepolarization: repolarization is interrupted by secondary depolarizations that may excite neighboring fibers and be propagated; experimentally induced by stretching, hypoxia
 - b. delayed afterdepolarization: after full repolarization occurs, V_m again transiently depolarizes; if the delayed afterdepolarization reaches threshold a premature propagated response will occur; experimentally induced by high concentrations of catecholamines or digitalis

G. Re-entry (see Fig.)

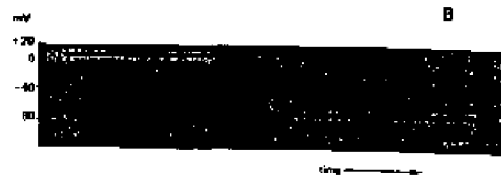
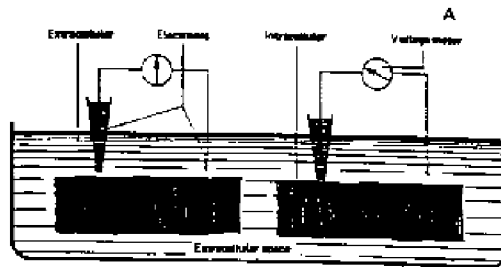
1. Definition: recirculating activations incited by an initiating depolarization
2. Required conditions
 - a. unidirectional block
 - b. slow conduction
 - c. length of loop $>$ ERP X Conduction Velocity
 - d. heterogeneity of impulses
3. Therapeutic aspect of antiarrhythmics: convert unidirectional block into bidirectional block; extend ERP of APs
4. Slow conduction in depressed area of heart mediated by depressed fast APs and/or slow (Ca-mediated) APs (Class I vs. Class IV antiarrhythmic agents)
5. Depressed fast APs and slow APs exhibit post-repolarization refractoriness---a situation that predisposes to re-entry

III SPECIFIC ANTIARRHYTHMIC AGENTS

A. Classification of antiarrhythmic drug (see Table)

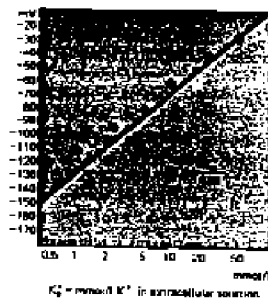
1. Class I: Na channel blockers (and K channels to some extent)
 - a. examples: quinidine, procainamide, disopyramide, lidocaine, phenytoin (diphenylhydantoin)
 - b. Depress phase 0 of fast AP
 - c. quinidine, procainamide and disopyramide prolong repolarization and ERP
 - d. quinidine depresses phase 4 depolarization and thus reduced automaticity
 - e. phenytoin particularly useful against digitalis-induced ventricular arrhythmias
2. Class II: beta-adrenergic blockade
 - a. example: propranolol
 - b. counteract (by competitive block) effects of norepinephrine, epinephrine (i.e., production of slow responses and enhanced automaticity)

3. Class III: prolong refractory period (mechanism unknown)
 - a. examples: bretylium, amiodarone
 - b. bretylium has been used as a "chemical defibrillator" when arrhythmia is resistant to standard methods
4. Class IV: Calcium channel blockers
 - a. examples: verapamil, diltiazem, nifedipine
 - b. block slow responses; slows A-V conduction (digitalis has similar effect by unknown mechanism)--hence useful to control impulse traffic in atrial tachyarrhythmias)

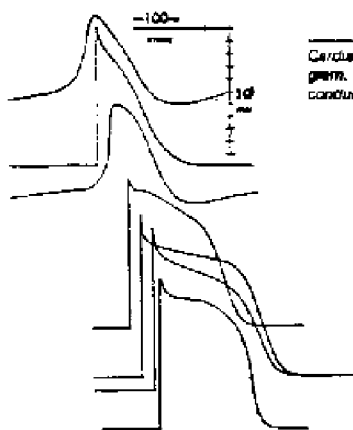


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Intracellular measurement of membrane potential. A. Diagram of the experimental arrangement. The space around the cell is filled with a saline solution with composition resembling that of blood. On the left, both recording and reference electrodes are extracellular, and the voltmeter measuring the potential between the two reads zero. On the right, the recording electrode has penetrated the cell while the reference electrode remains in the extracellular space. The meter now indicates the membrane potential. B. The potentials recorded before and after insertion of the recording electrode into the cell.

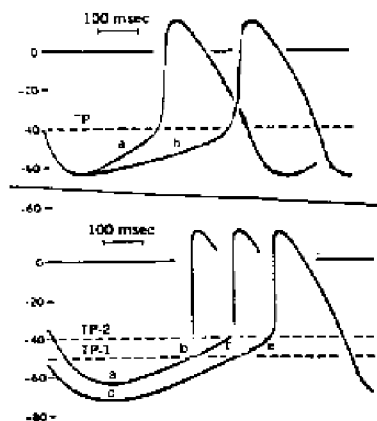
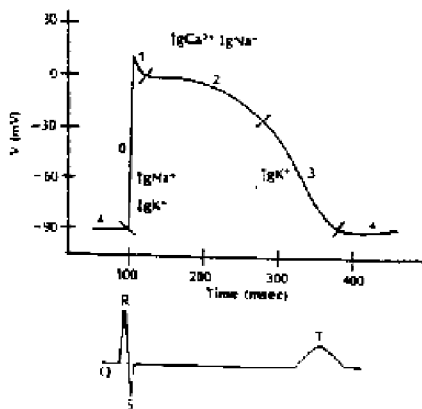


Dependence of the resting potential on the extracellular K^+ concentration. The abscissa shows the extracellular potassium concentration K^+ , plotted on a logarithmic scale; the ordinate gives the intracellularly measured membrane potential (mV) and the potassium equilibrium potentials given by the Nernst equation (red line) at the different K^+ . (From Adrian: *J. Physiol.* 133, 631, 1956)

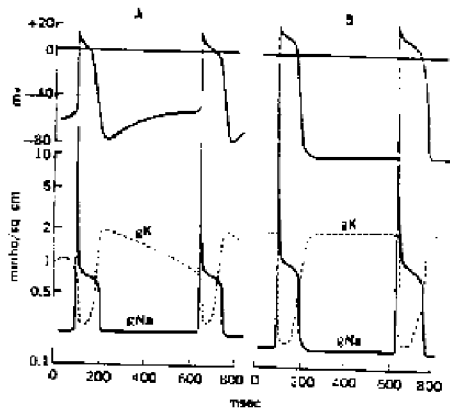


Tracings of typical transmembrane action potentials recorded from the following regions (from above downward): sinoatrial node, atrial muscle, atrioventricular node, bundle of His, Purkinje fiber in false tendon, terminal Purkinje fiber, and ventricular muscle fiber. Note sequence of activation at various regions and also amplitude, configuration, and duration of action potentials. (From Hoffman and Cronefield.)

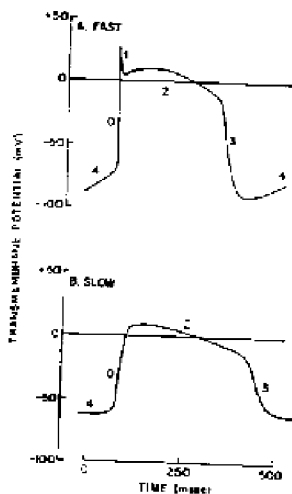
Cardiac action potentials recorded from a Purkinje fiber and a ventricular fiber. Phases of the action potential are indicated by 0, 1, 2, 3, and 4. Transfer conductance of an ion.



Drawings of transmembrane action potentials from fiber located in mammalian sinoatrial node to show ways in which frequency of pacemaker discharge can be altered. Upper diagram illustrates decrease in frequency of discharge caused by slowing of rate of diastolic depolarization from rate shown in a to that in d, resulting in increase in length of time required to reach threshold potential, TP, for generation of action potential. Lower diagram shows effects of reduction in level of threshold potential from 50 mv, TP-1, to 40 mv, TP-2, which results in slowing of rate. Also evident in this diagram is effect of change in level of "resting" potential from a to d, resulting in slowing of rate at discharge (see a-b, a-c, d-e). (From Hoffman and Cronefield.)



Schematic diagram of membrane sodium and potassium conductances (g_{Na} and g_{K} , lower traces) underlying pacemaker potential and action potential (upper traces). A, sinus node fiber; B, ventricular fiber from isolated rabbit heart. Note that "leaking" diastolic Na conductance is higher in sinus node than in ventricular muscle fiber. Also in sinus fiber, potassium conductance declines in diastole but remains at constant level in ventricular fiber. (From Trautwein, 11)



Diagrammatic representation of fast and slow responses from mammalian cardiac Purkinje fibers.

A. Fast Response. The phases of the normal fast response are shown: depolarization (0), repolarization (1, 2, 3), and the diastolic phase (4). Note the spontaneous phase-4 depolarization in this example. The rate of rise of phase 0 is rapid, and propagation will be rapid.

B. Slow Response. The slow response is initiated from a reduced flexa negative level of diastolic transmembrane voltage, shows slow depolarization, and has a long duration. Such an action potential propagates exceptionally slowly and leaves a long afterdepolarization.

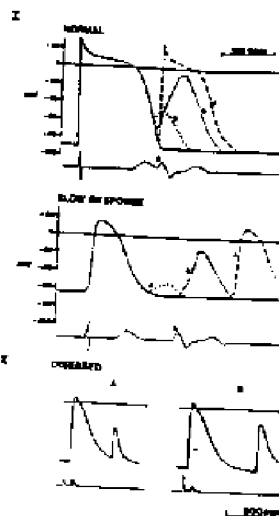
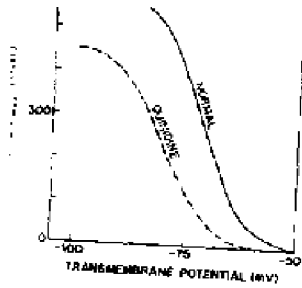
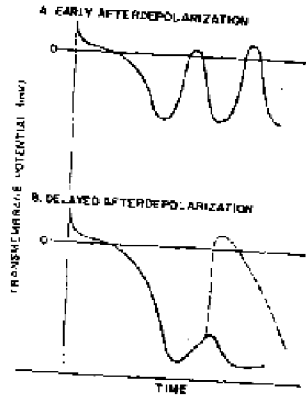
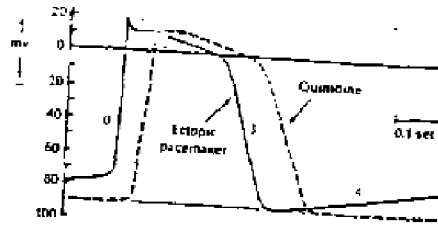


Fig. 3. Panel 1 shows schematic responses normal and partially depolarized (slow response) dog right bundle branch together with actual recorded surface electrograms to show time-course of refractoriness (postrepolarization ripples) in the latter. Responses A-C result from the introduction of spaced intervals during the cycle. A is the response that could be obtained on this delay of the "classical" refractory period; B, the imposed an action sufficient reduction in amplitude V_{max} to result in repetitive depression of conduction; C, the effects normally associated with the delay of the slow or which full recovery was within the normal fiber, recovery of excitability and consequent disappearance of refractoriness virtually complete completion of repolarization. In the partially depolarized fiber, on the other hand, refractoriness associated with repolarization (postrepolarization ripples) is increased to a more marked degree. Propagation of ripples beyond completion of repolarization increases the probability to invasion of ventricular territory to development of repetitive firing (atrial flutter) (page 4). Panel 2 shows an actual example of postrepolarization refractoriness in a specimen diseased human papillary muscle obtained from a dog with chronic rheumatic heart disease complicated congestive failure and high grade atrial and ventricular fibrillation. The specimen is the same as the one from a rabbit depicted in Fig. 11 were obtained.

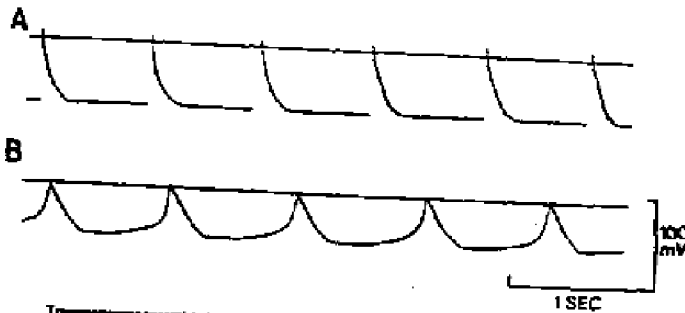


Membrane responsiveness.
 Membrane responsiveness in a cardiac Purkinje fiber is depicted. The maximal rate of rise of depolarization during phase 0 is plotted as a function of transmembrane voltage at the time of activation. The solid line shows the relationship under normal conditions, and the dashed line depicts the effect of a moderate-to-high concentration of quinidine. Quinidine shifts the relationship on its voltage axis so that a fixed response is obtained at any given level of transmembrane voltage. Also, the maximal rate of depolarization is reduced.

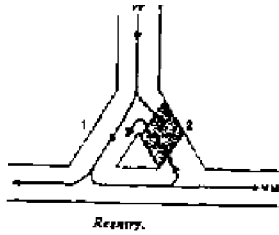


Two forms of triggered activity in a cardiac Purkinje fiber.

A. Early Afterdepolarization. Repolarization is interrupted by secondary depolarizations. Such responses may excite nearby fibers and be propagated.
B. Delayed Afterdepolarization. After repolarization is achieved, V_m again slowly depolarizes. If the delayed depolarization reaches threshold, a premature response can occur (dashed line).



Transmembrane potentials from level polarized, "fast response" (A) and low potential, "slow response" (B) fibers in a specimen of sheepdog heart (left atrial appendage). Maximum diastolic potentials (and associated for panel A and B were -72 mV (90 mV) and -66 mV (85 mV), respectively. Compare the large amplitude, rapidly rising action potentials observed from the normally polarized fiber with the low amplitude, slowly rising potentials from the partially depolarized cell. Also compare the membrane potential of the normal fiber in comparison during phase 4; whereas the partially depolarized cell begins to spontaneously depolarize in case its repolarization is complete, i.e., it has become automatic. Time and voltage calibrations are indicated in the lower right hand corner. See text for discussion. (Modified after Singer, Tse Eick, and Chou, '72)



The forms of reentry in the Purkinje fiber (Schomer and Erlanger, 1928-29). A branched Purkinje fiber (PF) terminates on a site of ventricular muscle (VM). The shaded area in branch 2 represents a demyelinated area that is the site of a one-way block. One orthograde sinus impulse is blocked in this area, but retrograde responses are propagated successfully. Retrograde conduction in branch 2 is slow enough for cells in branch 1 to recover and respond to the reentering impulse. A single reactivation of branch 1 will produce a single ventricular premature depolarization; continuous conduction around the circuit will cause ventricular tachycardia.

Antiarrhythmic drugs can abolish such reentrant activity by producing two-way block in branch 2 or by increasing conduction in branch 2, that is, by removing the one-way block.

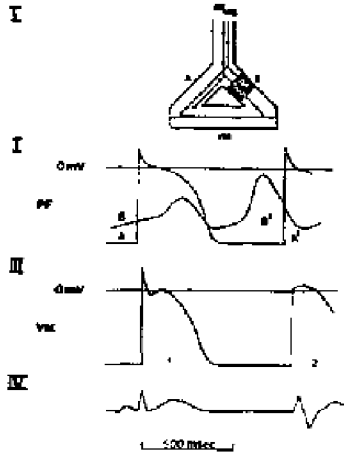


Diagram to show the possible mechanism for the development of self-sustaining ventricular dysrhythmias due to slow conduction and recovery in a branched segment of the Purkinje system and attached segment of ventricular muscle (VM). Slow retrograde propagation of ventricular muscle (VM) slow retrograde propagation. The main bundle of Purkinje fibers (PF) divides into two branches (A and B). Arrows indicate direction of impulse spread. Conduction is normal in both the PF and in branch A. There is a focal region of complete orthograde block due to slow conduction in branch B. Retrograde conduction occurs, although it is blocked only once. Action potentials from branch A and from the region of block in branch B are shown in traces A and B (see I; from VM in A and B). Note the low amplitude, slowly rising, slow response type action potentials recorded from the tip of block. Electrocardiograms showing reentry at three sites. The normally propagating action potential in A starts ventricular action potential in B in VM. The orthograde propagating action potential in B is blocked as being small and slowly rising. It undergoes complete decrement within the region of block and does not reach VM. The impulses from A find branch B sufficiently recovered to pass retrograde across (restoring sites B and A) reactivated a second time by the retrograde impulse with resultant generation of a premature ventricular. Note reversal of the sequence of activation of restoring sites A and B during the reentry as compared with the orthograde conducted beat. Suppression of this sequence of events could result in arrest as referred to as a circus movement that could result in reentrant ventricular fibrillation, including both ventricular tachycardia and fibrillation.

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS ACCORDING TO THEIR MECHANISM OF ACTION

CLASS	ACTION	DRUGS
I.	<i>Sodium Channel Blockade</i>	
A.	Moderate phase-0 depression and slow conduction (2+)	Quinidine, procainamide, disopyramide
B.	Minimal phase-0 depression and slow conduction (0 to 1+); shortened reexcitation	Lidocaine, encainone, tocainide, flecainide
C.	Marked phase-0 depression and slow conduction (4+); little effect on reexcitation	Flecainide, encainone, flecainide
II.	<i>B-Adrenergic Blockade</i>	Propranolol, others
III.	<i>Prolong Repolarization</i>	Amiodarone, bretylium
IV.	<i>Calcium Channel Blockade</i>	Diltiazem, verapamil

* Relative magnitude of effect on conduction velocity indicated on a scale of 1+ to 4+.

RELATIVE UTILITY OF ANTIARRHYTHMIC DRUGS IN THE TREATMENT OF SPECIFIC CARDIAC ARRHYTHMIAS *

ARRHYTHMIA	QUINI- DINE	PROCAIN- AMIDE	DISOPY- SAMIDE	LIDO- CAINE	PRIMY- TONE	PROPRA- NOLOL	VERE- LIUM	VERA- PAMIL
<i>Supraventricular</i>								
Atrial fibrillation, conversion	2	2	1	0	0	1	0	1
Atrial fibrillation, prophylaxis	3	3	3	0	0	2	0	2
Atrial fibrillation, rate control	0	0	0	0	0	2	0	3
Paroxysmal supraventricular tachycardia	2	2	2	0	1	3	0	4
Atrial premature depolarizations	3	3	3	0	1	3	0	2
<i>Ventricular</i>								
Ventricular premature depolar- izations	3	3	1	4	2	1	1	2
Ventricular tachycardia	3	3	2	3	2	1	2	1
<i>Digitalis-induced Arrhythmias</i>								
Atrial tachycardia with block	1	1	1	3	3	2	0	0
Nonparoxysmal A-V junctional tachycardia	1	1	1	3	3	2	0	0
Ventricular arrhythmias	1	1	1	3	3	2	0	0

* The relative values were based on an overall estimate of efficacy, convenience, and toxicity. The scale of relative utility is as follows: 0, none; 1, poor; 2, fair; 3, good; 4, excellent.