

# 丹参酮 II-A 磺酸钠对心肌电和机械活动的影响<sup>1</sup>

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**提要** 豚鼠、兔和猪离体心肌实验表明, T可抑制心肌收缩力; 缩短动作电位时程, 而对0相上升速率影响较小; 降低慢反应电位除极速率; 减慢窦房结细胞的自律性。提示T可能影响Ca<sup>2+</sup>向细胞的内流。另外, 实验结果还表明T对肌张力产生明显抑制的浓度(4μg/ml)小于对动作电位产生明显影响的浓度(40μg/ml)。

**关键词** 丹参酮 II-A 磺酸钠; 动作电位; 心肌收缩力; 心肉柱; 窦房结

丹参酮 II-A 磺酸钠(简称T)是从药用丹参中提取的脂溶性成份丹参酮 II-A, 又经磺化后所得到一种新的水溶性衍生物, 其结构式见图1。许多研究工作表明T具有抗心肌缺血缺O<sub>2</sub>的作用, 并对冠心病患者有一定疗效<sup>(1)</sup>。本工作观察了T对心肌电和机械活动的作用, 并探讨其机制。

## 材 料 和 方 法

豚鼠及兔, 击头致昏后取心脏, 置于35±1℃生理溶液中, 排尽瘀血后制备心房或心室肌条, 或窦房结部位的标本。猪, 电击致昏取心脏, 置于35±1℃生理溶液中数分钟, 排出瘀血后存放于4-8℃生理溶液中。在室温下摘取右心室肉柱, 1h内完成。所有实验动物♀♂不拘。

心肌标本固定于1ml容量的浴槽中, 以3ml/min灌流, 通100%O<sub>2</sub>。灌流液经一不锈钢6路阀切换。管道和肌槽内溶液的更换时间小于1min。紧靠标本安装一微型热敏传感器, 用数字温度计监视, 灌流液温度为34±0.5℃。通过两根尖端直径5-10μm的玻璃微电极进行

双极刺激, 以利于小标本的实验和减少伪迹。非自发活动的实验中刺激驱动采用恒压方波连续刺激, 方波的频率为0.5Hz, 波宽为1.5ms, 幅度为阈电位的1.5-2倍。用常规微电极细胞内记录方法记录细胞膜电位。同步记录肌张力, 使用悬臂槲式换能器, 静止张力调整在900±100mg。实验数据由微型计算机进行联机实时分析, 统计采用t检验。

所用T是上海第一制药厂产品; 维拉帕米(Ver)及盐酸肾上腺素(Adr)是上海天丰制药厂产品; 硫酸异丙肾上腺素(Iso)为北京制药厂产品。

生理溶液: Krebs-Henseleit液用于豚鼠心房、室肌和兔窦房结实验; Tyrode液用于猪心室肉柱实验。

## 结 果

### T对猪心室肌肉柱电和机械活动的影响

T的浓度为40和100μg/ml时, 使猪心室肉柱肌细胞的复极时程(APD<sub>50</sub>和APD<sub>90</sub>)缩短, 动作电位下的面积减少, 0相上升速率稍有降低。对动作电位的复极相进行概率密度分析, 以确定坪台期时程和坪台电位<sup>(2)</sup>, 结果发现T使坪台期时程变短, 坪台电位下降。在T的浓度为400μg/ml时呈现静息电位下降, 0相上升速率明显降低(表1)。T使心室肉柱收缩力减低, 且浓度减少至4μg/ml时仍有明显作用(表2)。在浓度-效应关系上小于使动作电位产生显著变化的浓度(图1)。图2是一典型的实验结果。

**T对慢反应动作电位的作用** 提高灌流液中K<sup>+</sup>浓度(K<sup>+</sup>)<sub>0</sub> = 18mmol/L, 刺激强度大于正常阈值4倍, 波宽8ms的电刺激也不能激

Tab 1. Effect of sodium tanshinone II-A sulfonate (T) on action potentials of pig ventricular cells. HPM = maximum value of probability density histogram of action potentials. HPD = potential of phase 2.  $\bar{x} \pm SD$ . Compared with control; \* $p > 0.05$ , \*\* $p < 0.05$ , \*\*\* $p < 0.01$

T( $\mu\text{g/ml}$ )	n	RP(mV)	APA(mV)	APD <sub>90</sub> (ms)	APD <sub>50</sub> (ms)	$\dot{V}_{\text{max}}$ (V/s)	HPM(%)	HPD(mV)
Control	9	-87 $\pm$ 5	115 $\pm$ 9	337 $\pm$ 23	255 $\pm$ 18	141 $\pm$ 19	51 $\pm$ 6	8.7 $\pm$ 2.9
4	4	-85 $\pm$ 6*	114 $\pm$ 10*	350 $\pm$ 38*	245 $\pm$ 43*	140 $\pm$ 22*	45 $\pm$ 9*	9.5 $\pm$ 3.6*
40	8	-82 $\pm$ 5*	107 $\pm$ 9*	332 $\pm$ 27*	240 $\pm$ 31*	130 $\pm$ 28*	46 $\pm$ 5*	7.9 $\pm$ 2.9*
100	8	-83 $\pm$ 5*	110 $\pm$ 9*	305 $\pm$ 27**	222 $\pm$ 26***	123 $\pm$ 39*	38 $\pm$ 5***	4.0 $\pm$ 5.8**
400	9	-76 $\pm$ 6***	100 $\pm$ 11**	280 $\pm$ 20***	192 $\pm$ 25***	80 $\pm$ 30***	36 $\pm$ 5***	5.2 $\pm$ 1.0**
Wash	6	-86 $\pm$ 4*	113 $\pm$ 10*	314 $\pm$ 32*	244 $\pm$ 29*	125 $\pm$ 12*	43 $\pm$ 6*	10.7 $\pm$ 3.5*

Tab 2. Effect of sodium tanshinone II-A sulfonate (T) on contraction of pig trabeculae carneaе cordis. PC = peak contraction. CD<sub>90</sub> and CD<sub>50</sub> = time to 90% and 50% relaxation

T( $\mu\text{g/ml}$ )	n	PC(mg)	CD <sub>90</sub> (ms)	CD <sub>50</sub> (ms)
Control	8	856 $\pm$ 137	389 $\pm$ 21	206 $\pm$ 19
4	4	673 $\pm$ 282**	421 $\pm$ 40*	206 $\pm$ 20*
40	7	489 $\pm$ 131***	353 $\pm$ 28**	196 $\pm$ 15*
100	7	437 $\pm$ 99***	384 $\pm$ 27*	202 $\pm$ 12*
400	8	333 $\pm$ 68***	291 $\pm$ 24***	167 $\pm$ 14***
Wash	6	558 $\pm$ 50**	374 $\pm$ 27*	230 $\pm$ 32*

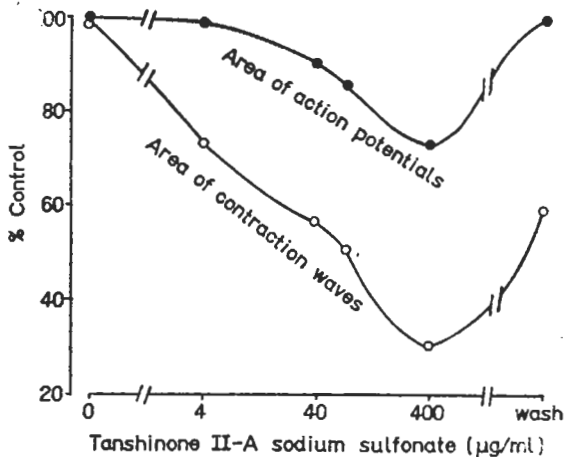


Fig 1. Effects of sodium tanshinone II-A sulfonate on action potential area and twice tension area of ventricular myocardium of pigs.

起豚鼠心室肌产生动作电位,证实此时快通道基本失活。Iso可使动作电位复又产生,其0相速率为 $11 \pm 2.5 \text{ V/s}$  ( $n=5$ ),为慢反应型,

加入T 40  $\mu\text{g/ml}$ 可降低慢电位的0相速率、振幅、面积,缩短APD<sub>50</sub>和APD<sub>90</sub>以及传导时间(图3)。对0相速率影响尤为显著,可能是明显延长传导时间的原因。

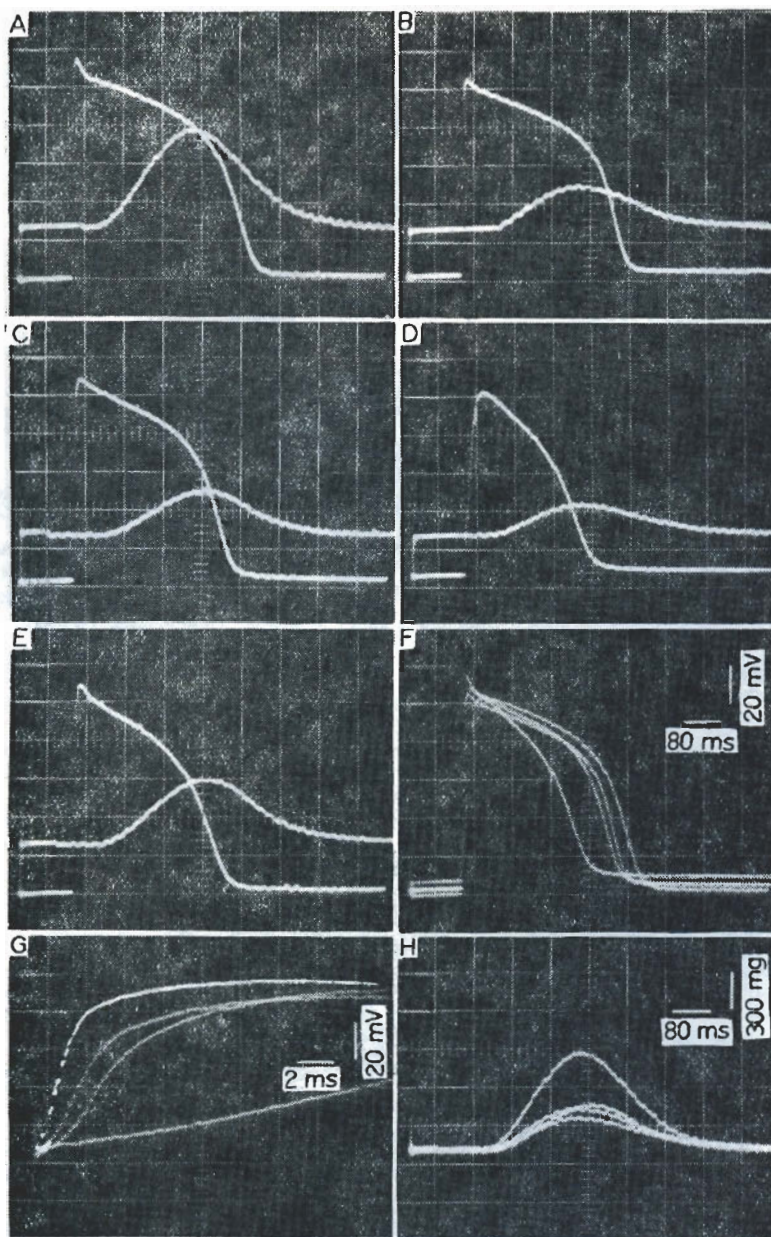
**T对兔窦房结自律动作电位的影响** T浓度4  $\mu\text{g/ml}$ 作用下,兔窦房结主导起步细胞自律动作电位的发放频率、振幅和面积均有降低,同时还伴有阈电位的提高(图4)。这种变化在药物作用约20 min后才趋于平衡状态。T浓度40  $\mu\text{g/ml}$ 时,5次实验中有3次经用药20 min后窦房结细胞自律动作电位消失。

**T对兔心房肌异常自律性的作用** 灌流液中加入Adr(0.1  $\mu\text{g/ml}$ ),可诱发兔心房肌产生快速自动去极化。合并使用T(40  $\mu\text{g/ml}$ ),则产生拮抗效应,使自动去极化频率下降(图5)。

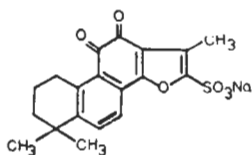
**Ver对心室肌细胞电和机械活动的影响** 已知慢通道阻滞药Ver(0.01-0.1  $\mu\text{g/ml}$ ),使猪右心室肉柱的动作电位波形发生变化,并明显抑制收缩力(图6)。与图2中波形相比,T使动作电位的复极相时程均匀地缩短,Ver却使其呈三角波形。

## 讨 论

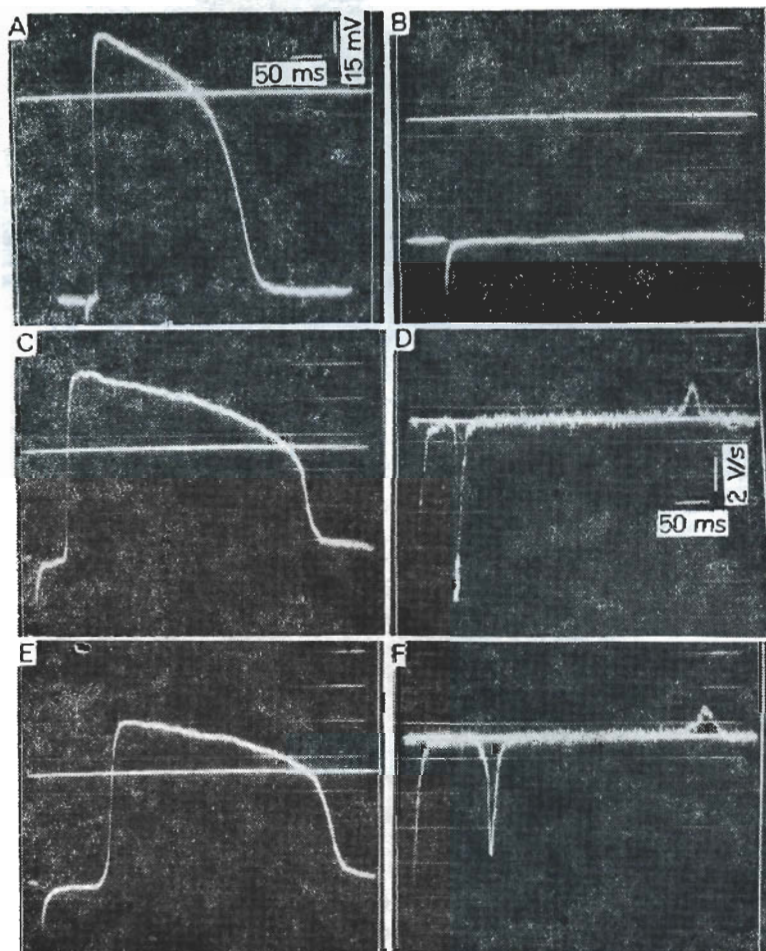
心肌细胞在兴奋时的慢相离子(主要为Ca<sup>2+</sup>)内向流动与心肌细胞动作电位的坪台期时程、坪台电位、面积和收缩力幅度有因果关系。T对这些参数均有抑制作用,因此推测T通过某种途径阻滞了慢通道,T使心室肌细胞慢



**Fig 2.** Effects of sodium tanshinone II-A sulfonate (T) on action potentials and twice tensions of ventricular myocardium of pigs. In A-E, the upper tracing is action potential, lower tracing, tension. A) control. B-D) 15 min after perfusion with T 4, 40 and 400  $\mu\text{g/ml}$ , respectively. E) 20 min after washout. F-H) superimposed photographs of A-D, for comparison, where F is action potential; G, corresponding phase 0; and H, twice tension. All records were made during a single cell impalement.



**Tanshinone II-A sodium sulfonate**



**Fig 3.** Effect of sodium tanshinone II-A sulfonate (T) on the slow response in guinea pig right ventricular cells. A) control. B) 5 min after perfusion of 18 mmol/L  $K^+$ -rich solution. C) control slow action potential in 18 mmol/L  $K^+$ -rich solution with isoprenalini sulfas 0.2  $\mu\text{g/ml}$ . D) control  $\dot{V}_{\text{max}}$  of phase 0. E) 15 min after application of T 40  $\mu\text{g/ml}$ . F) affected  $\dot{V}_{\text{max}}$  of phase 0.

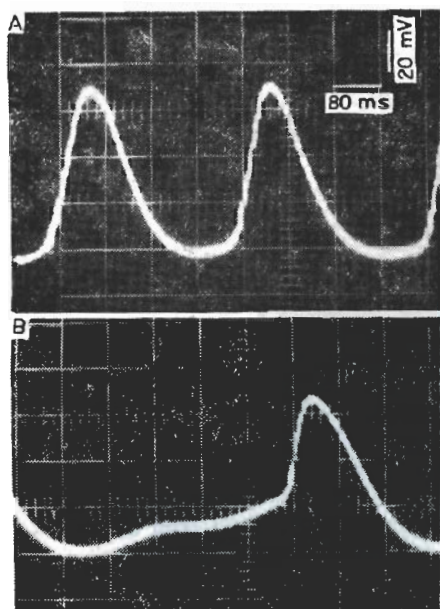


Fig 4. Effect of sodium tanshinone II-A sulfonate (T) on spontaneous action potentials of pacemaker myocardium in isolated rabbit sinus nodes. A) control. B) 20 min after perfusion with T 4  $\mu\text{g/ml}$ .

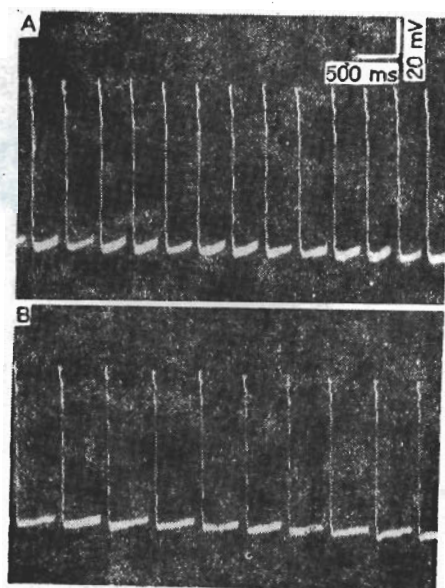


Fig 5. Effect of sodium tanshinone II-A sulfonate (T) on automaticity in rabbit atrial myocardium induced by adrenalin hydrochloridum 0.1  $\mu\text{g/ml}$ . A) Adr induced automaticity. B) 10 min after perfusion with T 40  $\mu\text{g/ml}$ .

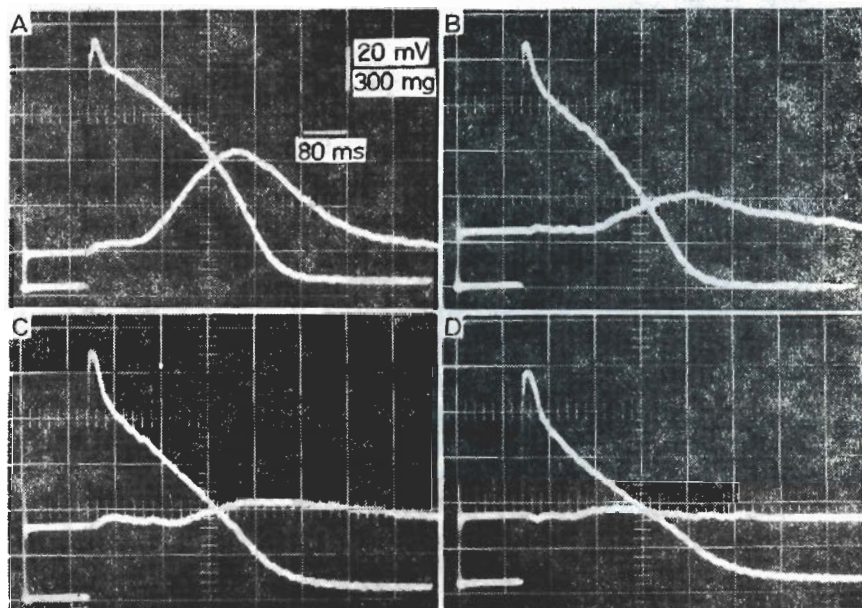


Fig 6. Effects of verapamil (Ver) on action potentials and twice tensions of ventricular myocardium of pigs. A) control. B-D) 10 min after perfusion with Ver 0.05, 0.5 and 1  $\mu\text{g/ml}$ , respectively.

反应电位的除极速度下降、慢反应传导减缓,该现象恰可部分反映  $Ca^{2+}$  电流  $I_{si}$  的减弱<sup>(3)</sup>. 任何  $Ca^{2+}$  通道的增强剂或拮抗剂,无论其作用是短暂的还是持久的,都将对起步细胞自律电位起明显影响<sup>(4)</sup>. 所以用  $Ca^{2+}$  通道受阻去解释 T 对窦房结细胞自律电位的压抑作用也似是适当的. 另外,Adr 通过 cAMP 激活心肌细胞膜上的磷酸化慢通道,相对增加了极化时的  $Ca^{2+}$  内流,使心房潜在起搏点的自发兴奋性加强. 对此, T 可起拮抗效应,由于 T 不具备与交感胺受体结合所必需的化学结构,因此 T 的这一效应不是通过受体传递,而很有可能是直接影响了  $Ca^{2+}$  的内流. T 对  $Ca^{2+}$  的阻滞作用是否为竞争性的,本文未进行此方面的工作. 对照性实验已表明 T 的药物作用效价较慢通道阻滞剂 Ver 为低.

Nifedipine 和 diltiazem 的效应随灌流液的清洗可较迅速消失, Ver 却难于通过清洗完全消除影响. 据此可推测前二药物作用于细胞膜外表面,而后一药物直接或间接地作用于细胞内<sup>(5,6)</sup>. 本工作中观察到 T 作用具有可逆性,它亦可能作用于膜外表面的某些位点影响慢通道.

据本工作, T 对心室肌动作电位和心肌收缩力的作用存在浓度差异,即抑制心肌收缩力

较抑制电活动的浓度约小 10 倍. 这与 Patmore 等的实验结果<sup>(7)</sup>相近似. 这种差异提示 T 的负性肌力作用除通过影响慢通道以外可能还有其它途径.

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## Effects of sodium tanshinone II-A sulfonate on electrical and mechanical properties of myocardium<sup>1</sup>

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**ABSTRACT** Tanshinone II-A was extracted from the root of *Salvia miltiorrhiza* Bunge. Its sodium sulfonate (T) is water soluble and used in this experiment, Cell

membrane potentials in sinoatrial node, atrium and ventricle were recorded by microelectrodes. T shortened the duration of the action potentials with little influence

on phase 0 and suppressed slow response and sinus automaticity. Synchronous recordings of myocardial contraction with cell membrane potentials in pig trabecular carnae cordis revealed a simultaneous alteration of mechanical ( $T = 4-400 \mu\text{g/ml}$ ) and electrical ( $T = 40-400 \mu\text{g/ml}$ ) activities. The results suggest that T influences the inward  $\text{Ca}^{2+}$  current, while the evidence of the separation between two dose-response relationships of electrical and mechanical

activities implies another mechanism corresponding to negative inotropic effect of T rather than  $\text{Ca}^{2+}$ -antagonism.

**KEY WORDS** sodium tanshinone II-A sulfonate; action potentials; myocardial contraction; trabecular carnae cordis; sinoatrial node

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