

心脏机械电反馈 与心律失常

从基础到临床

CARDIAC MECHANO-ELECTRIC
FEEDBACK & ARRHYTHMIAS

From Pipette to Patient

PETER KOHL

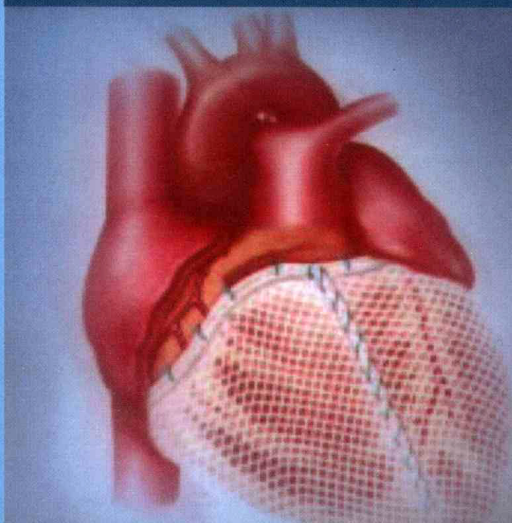
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王立群 程龙献 郭继鸿 主译



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Atrial Fibrillation and Dilated Cardiomyopathy

译者序

虽然本书的译稿已收笔,又轮回我撰写中文版前言,但心中诚惶诚恐的紧张仍无丝毫的减轻和解脱。仍在担心交出的稿样不能通过验收,担心出版后,乘兴而来的读者却扫兴而去,众望所归变成众人失望。

3年前,天津科技翻译出版公司的编辑同志将此书交给我时,大致浏览了全书后,那些前沿而又与临床紧密结合的内容让我兴奋了,我拍着胸脯自信地说:“中国学术界太需要引进这本书了,我们一定用最短时间,用最好的质量完成翻译,不负重托。”结果我失言了,两年过去了,译文仍不能脱稿,几次电话之后,出版社的同志已不好意思启齿催稿了。

译稿的拖延除主观因素外,不少客观因素也严重影响着全书翻译的进度。首先,机械电反馈的研究纯属一个跨学科的新领域,其很多内容都与物理学、机械学、力学等相关,还包括了不少难懂复杂的计算公式,这些对于临床医生是陌生甚至是遥远的。译者对这些内容的理解十分困难,使翻译出现了意想不到的障碍。其次,机械电反馈是近年来才引起医学界关注的前沿科学,这一新兴学科的内容深奥,理论难懂,论述晦涩,内容与文字上的双重困难曾使翻译几乎进入绝境。再者,本书的副标题为“从基础到临床”,说明本书是将基础科学与临床医学有机地作为一个整体而论述。而基础部分占主体,超过了全书的50%,这些边缘、跨学科的基础研究内容对从事临床医学的译者而言也充满了荆棘与挑战。

有志者事竟成,几位译者凭借百折不挠的毅力,又一次用超人的努力,完成了本书艰辛的翻译工作,再次验证了这一千年古训的魔力。实际上,引进的每本书的译者就是该书在国内的最初读者。在翻译与阅读之中,我们深感到:本书的3位主编Kohl、Sachs及Franz是

这一领域的先驱与巨匠,他们卓有成效的研究成果是这门新兴学科乃至本书的基石,他们是名副其实的大师与学术权威,他们深邃的洞察力及犀利的学术敏感性让你感到震撼。我们深感到,机械电反馈的理论观念对当今传统心律失常的发病机制和有效治疗的选择等方面都有重要的启迪,甚至是冲击。机械电反馈在心脏电和机械的病理性重构中都将起到十分重要作用。很多心律失常,例如心房颤动、室性心律失常的发生中机械电反馈机制都起到了肯定而重要的作用,大量的资料已证实机械电反馈对心脏电活动有着独立的调整作用。因而抑制和减弱这一作用,降低心脏的机械负荷,必然能起到治疗心律失常的作用,近年来应用RAS系统的抑制剂(ACEI、ARB)等预防与治疗心房颤动,能有效降低致命性室性心律失常引发的猝死等,都是基于这一新理念。

此外,机械电反馈在心血管病的病理生理学的作用也是异军突起,备受重视,不少的传统概念因此而将被更改或得到补充,以朋氏反射(Bainbridge reflex)为例,过去认为朋氏反射是体内单纯心血管范围的神经反射性调节,但在离体心脏或去神经的动物模型证实朋氏反射依然存在的事实提示机械电反馈在其中的独立作用。本书的最大学术贡献凸显在两个方面:其一,本书把近年来这一领域的进展集为一体,展现给读者;其二,本书通过基础与临床的结合,对原来模糊难懂甚至抽象的机械电反馈做了令人易懂而又令人信服的阐述。

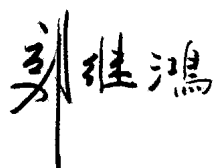
国内的机械电反馈的研究已有近10年的历史,但研究都是小规模,零散而不集中,与国外水平相差甚远,需要进一步的提高和发展,而更重要的是国内一般医师对这一新领域的知识几乎还是空白,需要填补,因此,本书中文版的出版有着极其重要而不能低估的意义。

本书出版之际,要特别感谢出版社的果断选题、理解和支持。还要感谢全体译者,是集体的精诚合作使本书最终如愿出版,尤其要感谢主译王立群,其担当了全书约 50%的文稿,为本书的出版荣立头功,另一位主译程龙献教授不仅是国内机械电反馈研究的先行者,而且是本书翻译的中流砥柱。

尽管译者已尽了最大努力,但中译本肯定还会有大量的纰漏,甚至错误,恳请读者予以

谅解并不吝赐教,以便使谬误能及时纠正。

今天正值上海世博会开幕之日,使本书增添了与世博同行的风采。

A handwritten signature in black ink, reading '刘继鸿' (Liu Jiahong). The characters are written in a cursive, flowing style. The first character '刘' is on the left, followed by '继' and '鸿' on the right. A vertical line runs through the middle of the characters.

2010年4月30日

于北京

序 言

心脏调控观点的拓展

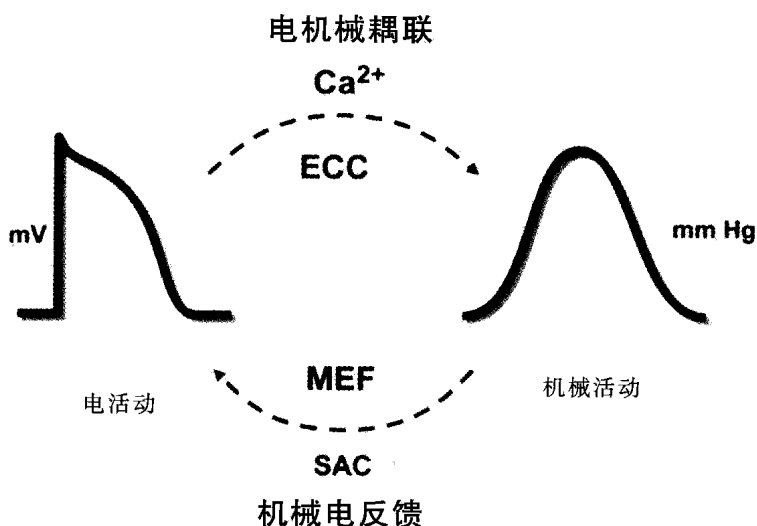
电冲动的转导引起肌肉收缩频率和机械强度的变化称为兴奋收缩耦联(ECC),这是理解心脏病的基础和临床必不可少的基本概念。兴奋收缩耦联中的神经递质(包括儿茶酚胺和其他许多调质)能够明显影响细胞内钙的调节,从而使心肌行使其功能。钙调节能影响肌动蛋白和肌球蛋白的相互作用,调节血流动力学,以适应心脏年复一年的节律跳动。

有一种观点认为,作为 ECC 的互补调节,心脏机械功能随神经和激素的改变而改变,从而影响心脏兴奋和传导。也就是说,尽管机械电耦联或反馈(MEF)还是一个尚未成熟的理论,但它在生理学和病理生理学中的作用已成为当代生物学上令人感兴趣的内容。机械刺激改变心脏电特性的机制和途径现已成为衡量治疗性心脏调控新方法发展的重要尺度。

下图显示了一个简单而实用的新观点,即

双向动力观点。尽管兴奋收缩耦联在当前的治疗策略中已为人们所熟悉,但是机械电反馈直到近些年才引起医学界的兴趣。虽然已经证明兴奋收缩耦联异常是多种心脏疾病(如不同类型的心肌病)的重要发病机制,但尚未证明机械电反馈在其中起着同样重要的作用。随着急性慢性心脏重塑机制研究的深入,机械电反馈的作用开始日益显现。舒张性心力衰竭、房颤和心肌梗死后瘢痕形成是引起心脏重塑最为常见的原因。我们推测机械电反馈在电和机械病理重塑中都在发挥作用,但这种观点却缺乏直接的证据。尽管对某些问题(如 MEF 如何促进正常生理过程)我们已有初步认识,但其如何参与疾病的预防和转归尚未明确。

MEF 相关内容晦涩难懂却又十分重要,本书对其作用的阐述向前迈进了重要一步。书中汇集了当前该领域中许多杰出学者的前沿思



心机的机电耦联与机械电反馈关系的概念示意图。电活动和兴奋收缩耦联受众多信号转导途径的调节,这些信号转导途径影响细胞内的钙浓度,并能激活和改变肌动蛋白-肌球蛋白间的相互作用。多数情况下,牵张激活离子通道(SAC)既能调节机械刺激(如张力、长度及方位变化等)改变心脏电功能的途径,又能影响细胞内的电位和电兴奋。(Modified from a figure provided by Michael Franz, with permission.)

想及优秀成果,能让读者明显体会到 MEF 作为重要科研课题的时刻到来了,并为今后的研究指明了方向。本书的三位编者是这个领域的先驱,他们选择相关主题,对当前的研究进行了精辟的总结。MEF 的研究带头人在许多 MEF 重要国际性研讨会中探讨了该领域中的突出问题,本书继续讨论了这些话题。综合和提炼这些内容有利于更好理解文章中涉及的重要观点,这些观点源自基本生理学理论、全面认识心脏调控及新治疗靶点的探索。

MEF 的经典研究及 MEF 如何促进以下事件的发生尚在探讨中,包括斑布里奇(Bainbridge)反应、牵张激活性通道的功能及心脏震荡的致命现象等。此外,新 MEF 指数的测定广泛运用了分子技术、生物物理技术及遗传学技术。书中不仅涵盖了 MEF 潜在的作用、影响及意义,还为未来的研究方向提供了线索。

本书的开头部分阐述了心脏电反馈的核心概念及许多有趣的临床表现。不同的读者可能有不同的阅读重点,有些读者对 MEF 的急、慢性影响感兴趣,而另一些读者则对房颤及其他心律失常的内容感兴趣。书中描述了 MEF 变化如何决定疾病的转归,并且还涉及了一些少见的内容,包括不同心脏细胞(如心肌细胞和心脏成纤维细胞)中 MEF 的作用以及有关部分膜性心脏细胞结构的新问题。

近来人们认为,丝状细胞骨架蛋白结构的

改变是单基因遗传性心律失常和少见心肌病的重要致病因素。然而,我们在细胞或生理水平对其基因型的了解还不多。MEF 是否受到细胞表面受体和信号复合物的部分调节、能否与不同的离子通道亚单位相互作用还不十分明确。最后读者会发现,研究者应用新方法解决仍然悬而未决的问题,例如,细胞间电生理的变化如何影响特殊蛋白的表达,从而决定“谁对谁说什么”的信号传递过程。

最后,我想表达一下个人观点:ECC 与 MEF 间机械及电调控整合的深入研究可能为顽固性心脏疾病尤其是致命性心律失常的治疗和预防提供新的线索。即便以上观点有失偏颇,但我仍觉得在更大范围和更高水平对心脏 MEF 的科研工作予以关注很有价值。虽然人们对心电紊乱的治疗进行了数十年的尝试,但目前的治疗和预防手段都极其有限,存在的问题主要是治疗方法的有效性及其副作用或费用-效益评价的难度逐渐增加。尽管对心律失常的治疗迫切要求改进,但是仍有必要通过心脏调控方面的基础研究来促进临床治疗方法的发展。本书阐述了这些进步如何成功取得及其潜在的应用价值。

PETER M. SPOONER, PHD

于巴尔的摩

前言

心脏机械电反馈:从基础到临床

Peter Kohl, Frederick Sachs, Michael R. Franz

心脏是机械敏感性器官。

牵拉心肌组织能引起心肌结构和功能特性的改变,包括基因表达、蛋白质周转、结缔组织性质、电机械耦联、收缩性和电生理特性的变化。本书着重讨论机械刺激直接或间接对心率及心律的影响。

牵张心肌可产生多种效应,如心率能随静脉回流量的改变而改变;机械牵张可诱发室性早搏和快速性心律失常;心脏的容量和压力超负荷或机械刺激可引起心律失常。

对心脏机械敏感性的报道可追溯到一个世纪前。1763年,Akenside对一例猛击心前区导致心律失常的病例进行了报道,该患者伴有严重的组织创伤^[1]。1882年Riedinger等注意到,在没有组织损伤的情况下,猛击胸壁也可以诱发心律失常,如心脏震荡^[2]。1915年,Bainbridge提出了机械刺激加快心率的著名观点^[3]。5年后,Schott将胸前叩击作为斯-亚病患者在完全性房室传导阻滞期间保持意识清醒的有效方法^[4]。

进行过Langendorff心脏灌流等实验操作的生命科学系的学生熟悉心脏机械敏感性的概念。从字面上理解Langendorff心脏灌流,即心跳在静止状态下可以被手指敲击启动。心外科医生利用类似的敲击能使停跳的心脏重新跳动。

这些现象潜在的机制是什么?是否有方法对它们进行定量研究?心脏机械敏感性是否有概念性框架?

后一个问题最好以调节理论为基础进行解释。调节理论认为,机械敏感性是任何机械

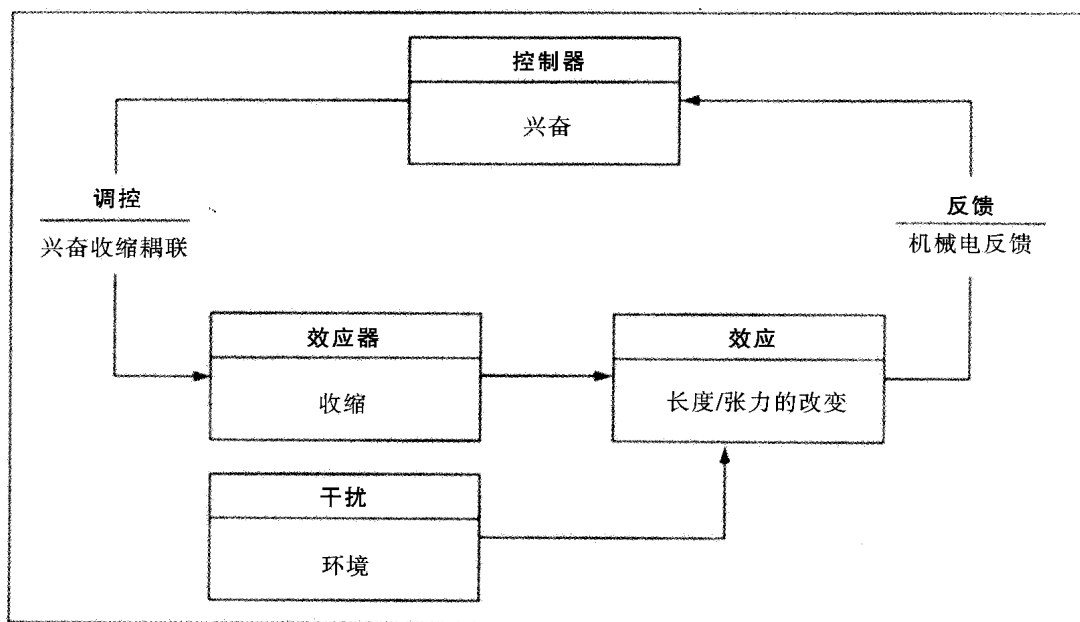
电控体系都具有的共性,而非一种特性。如图所示,机械电反馈与兴奋收缩耦联形成一个闭合回路。1967年,Kaufmann和Theophile首先将这一观点应用于心房和心室多细胞的实验中,在牵张诱导下,细胞的自发自律性及异位自律性增强,他们将观察到的现象称为MEF^[5]。

人们应用细胞内/外电记录的方法探寻心脏机械电反馈的机制。单相动作电位的记录对研究完整心脏的牵张效应最有帮助。跨细胞膜记录能区别不同细胞(包括起搏细胞、心房细胞和心室细胞)的牵张激活离子通道。首个通道选择性阻滞剂的发现让人们开始了解MEF机制的临床意义。先进的光成像技术和分子生物学技术有助于进一步研究钙调节和第二信使(例如NO)在心脏机械电反馈中的作用。

急性牵张效应已得到充分的证明,但是慢性心脏病理变化(包括机械诱导的电重塑和结构重塑)的机理颇为复杂且受多种因素的影响,故建立一条因果链式反应比较困难。

大量的证据证明腔室扩张对房颤的形成起关键作用。同样,心衰和心室超负荷时发生的心律失常与机械刺激有关。由此可知,降低心肌张力(例如使用利尿剂、减轻后负荷以及植入心脏辅助装置)和进行心脏再同步治疗有利于改善心脏泵功能及电生理活动。现已证明心脏功能的各方面都与心脏机械环境相关,所以今后的研究方向应该更多揭示这些现象的特殊机制。

心脏的机械敏感性及其在电活动中的作用无疑形成了一个非常复杂的系统。尽管本书



本图显示了心脏电机械调节环。电兴奋调节心脏的兴奋收缩耦联。细胞长度和(或)张力的改变通过机械电反馈影响心肌的兴奋性。MEF 的发生不依赖于机械效应是否由心脏收缩本身引起，而是依赖于心脏自身机械环境的改变。在没有 MEF 的情况下，这个系统将不稳定。(From Kohl P, Hunter P, Noble D: Stretch-induced changes in heart rate and rhythm: Clinical observations, experiments and mathematical models. Prog Biophys Mol Biol 71 (1):91-138, 1999, with permission.)

对 MEF 的很多方面进行了整理,但是其详尽的机制、生理作用和临床意义还有待深究。

我们非常感谢在机械电反馈研究中做出贡献的学者们。他们所从事的是跨学科且长期以来不为人们重视的工作。从大肠杆菌到心肌细胞,从建立计算机模型到临床实践,从心律失常原因不明到提供潜在的治疗靶点,MEF 得到了很大的发展。

本书将基础科学与临床研究结合起来,对 MEF 原本模糊的现状进行了最新的论述。这对更好地理解心脏是完整的电机械闭环体系具有潜在而深远的意义。编者希望读者能从中得到启发,并激发人们对机械敏感性心脏的未知领域进行更深入的探索。

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