·外籍华人专稿·

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Precision medicine is ammunition for anesthesiologists to improve patient outcomes during the perioperative period: genetic variability of beta-blockers and opioids

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【Abstract】 The evolving practice of precision medicine allows physicians to make disease treatments and prevention decisions based on a patient's individual genetic and molecular profile. In recent years, gene sequencing and related techniques are becoming more affordable and more accessible to healthcare providers, and their use in various medical fields continues to expand. In particular, there are numerous opportunities for the use of precision medicine in the perioperative setting. For example, individual polymorphisms in alpha and beta adrenergic receptors can improve the efficacy of beta blockade, or predispose a patient to adverse drug reactions including hypotension and bradycardia. Likewise, particular polymorphisms in opioid receptors can increase or decrease the effectiveness of various opioid medications for achieving adequate postoperative analgesia. In addition, mutations in the cytochrome P450 2D6 (CYP2D6) enzyme can drastically affect the clinical response to a particular subset of beta blockers and opioids by accelerating or decelerating their metabolism and clearance. Preoperative genetic testing would allow anesthesiologists to identify these and other relevant molecular characteristics in their patients, and choose appropriate perioperative therapies accordingly in order to maximize clinical outcomes while minimizing the incidence of adverse events. It is the time for anesthesiologists and perioperative care providers to practice precision medicine.

【Key words】 Precision medicine; Perioperative period; Beta-blockers; Opioids

围手术期精准医疗有助于麻醉医师改善患者预后：β受体阻滞剂与阿片类药物的遗传变异性

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【摘要】 随着精准医疗的不断发展，医师能够根据患者的个体遗传和分特征制定疾病的治疗和预防策略。近年来，基因测序及其相关技术在医疗机构中变得更加经济和便捷，其在各种医疗领域中的应用范围也在不断扩大。特别是在围手术期，有很多使用精准医疗的机会。例如，α 和 β 肾上腺素能受体的个体多态性可提高 β 受体阻滞剂的疗效，同时也使患者容易出现药物不良反应，包括低

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血压和心动过缓等。同样，阿片受体的个体多态性可以使阿片类药物在术后镇痛中的有效性提高或者降低。此外，细胞色素 P450 2D6(CYP2D6)酶基因的突变可以通过加速或减缓 β 受体阻滞剂和阿片类药物的代谢和清除，大大影响到二者的临床反应。术前基因测序可使麻醉医师识别患者上述以及其他相关的分子特征，并相应地选择适当的围手术期治疗策略，从而最大限度地提高临床疗效，减少不良事件的发生率。当下正是麻醉医师和围手术期医务人员实践精准医疗的时候。

【关键词】　精准医疗；围手术期；β 受体阻滞剂；阿片类药物

The Development of Precision Medicine

The Philadelphia Chromosome and its association with chronic myeloid leukemia (CML) were first described in 1960 by observation of chromosomal structures under a microscope[1], and later characterized as a reciprocal translocation using chromosomal banding techniques in 1973[2]. Its gene product, the breakpoint cluster region-Abelson murine leukemia viral oncogene homolog (BCR-ABL) protein, is a constitutively expressed tyrosine kinase that activates a cellular signaling cascade, which leads to unregulated cell division and inhibition of DNA repair[3]. In the 1990's, a group of scientists in Switzerland used high-throughput screening of chemical libraries to identify a drug that could inhibit the hyperactive BCR-ABL protein[4]. After refinement and testing they ultimately developed the chemotherapeutic agent imatinib, which was FDA approved in 2001 for the treatment of CML. Since the use of imatinib and other targeted treatments, the 5-year survival rate for CML has doubled from 31% for people diagnosed in the early 1990's to 63% for those diagnosed between 2005 and 2011. Moreover, the 5-year survival rate for patients consistently taking imatinib has been 90%[5].

The development of imatinib and its use in the treatment of CML represent one of the earliest examples of the use of medical therapy targeted to a patient's specific genetic profile, and embodies a broader approach to medicine, which has progressively become more focused on individual patients rather than populations. Driven by the success of the human genome project, explosive growth in new diagnostic technologies has been seen in the last two decades. As technology has continued to advance, so has our ability to identify genetic and bio-molecular variations not only between disease processes, but also between individual patients. Genotyping can be performed to look for particular variations of known genes, or exome sequencing can be done to identify only protein-coding genes. Indeed, even the cost of sequencing an individual's entire genome has dropped from $50 million in 2003 to under $1,000 in 2016, and can now be performed in just one day[6].

Healthcare providers now find themselves faced with a new challenge: how to use these novel technologies to provide better care for their patients, to improve outcomes, and to maintain cost-effectiveness at a population level. The term precision medicine has recently emerged to describe the evolving practice of disease treatment and prevention that takes into account individual genetic and molecular variations. It involves the integration of molecular and clinical data from individual patients in order to develop a more accurate taxonomy of diseases, which can subsequently be used to enhance diagnosis, disease progress prediction and treatment.[7]. In 2015, U. S. President Barack Obama established a new framework for the development and application of precision medicine called the Precision Medicine Initiative (PMI). This initiative was backed by a $215 million investment to support research, development, and innovation in the field of precision medicine, and included: $130 million to the National Institutes of Health (NIH), U.S.A., for development of a voluntary national research cohort of a million or more volunteers to propel our understanding of health and disease; $70 million to the National Cancer Institute, which is also part of NIH, to scale up efforts to identify genomic drivers in cancer and apply that knowledge in the development of more effective approaches to cancer treatment; $10 million to the Federal Drug Administration to acquire additional expertise and advance the development of high quality, curated databases to support the regulatory structure needed to advance innovation in precision medicine and protect public health; and $5 million to the Office of the National Coordinator to support the development of interoperability standards and requirements that address privacy and enable secure exchange of data across systems.[8].

Many examples now exist of the use of precision medicine in patient care, with varying degrees of success. For example, ivacaftor was developed as a treatment for cystic fibrosis patients with the G551D mutation, and works by binding to the non-functional chloride channel in such a way as to facilitate non-conventional gating in order to increase chloride transport through the channel[9]. Another pharmaceutical agent, trastuzumab, was developed to target a specific oncogene product (much like imatinib), human epidermal growth factor receptor 2 (HER2) receptor found in a

particular subset of breast cancers[10]. Precision medicine was used in both of these cases to create unique medical products for an individual group of patients, but more often it entails the selection of what is likely to be the most appropriate therapy from an array of existing options. In particular, certain mutations in cytochrome P450 enzymes can be used to predict warfarin and clopidogrel sensitivity and specific mutations associated with thoracic aortic aneurysms can help determine appropriate thresholds for surgical intervention[11]. New research and new discoveries continue to facilitate our ability to tailor medical therapies to each individual patient, and new technologies in molecular biology and information technology continue to make that process more streamlined and affordable. In the following sections, we describe two examples that are applicable to the perioperative period for anesthesiologists and perioperative care providers to improve patient care.

Precision Medicine in the Perioperative Period: Beta-Blockers

Precision medicine is often thought of in the context of malignancy and other chronic disease. Approaches to precision medicine have, in these cases, been used to identify novel therapeutic targets or susceptibilities to particular medical therapies with the general goal of prolonging survival or improving chronic morbidity. Perioperative medicine, in contrast, is practiced within a short-time course immediately before, during, and after surgery. However, new research continues to suggest that there are nevertheless opportunities to improve patient outcomes in the perioperative period through the use of precision medicine.

One such example involves the use of perioperative beta blockade to reduce the incidence of adverse cardiac events and cardiac mortality in patients undergoing non-cardiac surgery. Systemic sympathetic activity is increased under surgical stress, leading to increased heart rate, contractility, and myocardial oxygen consumption. The purpose of beta blockade is to attenuate this response in order to reduce the risk of ischemia for high risk patients during the perioperative period, and was originally supported by data from Mangano et al. in 1996, which demonstrated that perioperative atenolol reduced perioperative myocardial ischemia by 50%, and the incidence of cardiac death by 10%[12]. The DECREASE trial, which was published in 1999, identified 112 patients with stress-induced ischemia during dobutamine echocardiography who were undergoing high risk vascular surgery, and randomized those patients to receive bisoprolol starting one week before surgery and extending 30 days post-operatively compared with standard care[13]. The results included a 13.6% reduction in 30-day cardiac death in the bisoprolol group (3.4%) compared to the control group (17%), as well as a 17% reduction in non-fatal MI (0% vs. 17%). These findings prompted liberal use of beta blockade in the perioperative setting, especially for patients with multiple cardiac risk factors as measured by the Revised Cardiac Risk Index (RCRI)[14]. Of note, the DECREASE trials are found to violate ethical and scientific standards and the leading researcher, Don Poldermans, was found to commit scientific misconduct and was dismissed from his position at Erasmus Medical Center in Netherlands.

Those results were more recently complicated by the POISE trial, in which researchers randomized 8351 patients with atherosclerotic disease undergoing non-cardiac surgery to receive either metoprolol or placebo two to four hours before surgery followed by another dose zero to six hours after surgery and then daily for 30 days postoperatively. They found a modest 1.1% reduction in cardiovascular death, non-fatal MI, and non-fatal cardiac arrest in the metoprolol group (5.8%) compared to the control group (6.9%), along with a statistically significant increase in total mortality and stroke (3.1% vs. 2.3% and 1% vs. 0.5% respectively)[15].

Perioperative beta blockade remains a controversial topic, but what is now being discovered is the considerable inter-individual genetic variability in adrenergic receptors and enzymes involved in the metabolism of beta blockers, and how those differences may affect the clinical response to pharmacologic therapy.

Cardiac β_1 adrenergic receptors, when stimulated by an appropriate ligand, affect a downstream signaling cascade that results in the activation of adenylyl cyclase, which ultimately increases cardiac inotropy and chronotropy. Thus, mutations that alter the β_1 receptor functionality could potentially alter the physiologic response to receptor blockade. For example, the frequency of β_1 Arg389 is approximately 70% in Caucasians and 50% in African-Americans, compared to 30% and 50%, respectively, for the β_1Gly389 polymorphism[16]. However, the β_1 Arg389 polymorphism results in three-fold greater agonist-induced stimulation of adenylyl cyclase compared to β_1Gly389, greater basal cardiac contractility, and more pronounced beta-blocker responsiveness[17]. Moreover, this particular mutation confers an improved mortality outcome in response to beta blockade with bucindolol for heart failure patients[18].

$Beta_2$ adrenergic receptors, which are primarily expressed on smooth muscle cells of the airway and vasculature, also have a limited presence on cardiac myocytes. The functionally distinct β_2Ile164 polymorphism causes

uncoupling of agonist-induced adenylyl cyclase stimulation and is associated with decreased exercise capacity and increased mortality in heart failure patients[19]. Furthermore, β_2 adrenergic receptor polymorphisms at positions 79 (C to G) and 47 (G to A) have both been shown to be independently associated with improved mortality in acute coronary syndrome patients discharged on beta-blockers[20].

Alpha$_{2A}$ and α_{2C} adrenergic receptors located at the presynaptic nerve terminal inhibit the release of norepinephrine when activated by endogenous catecholamines, such as epinephrine; whereas presynaptic β_2 receptors facilitate the release of norepinephrine. Their native expression helps to regulate activation of post-synaptic β_1 and β_2 receptors on the cardiac myocytes, which act to increase inotropy and chronotropy[16]. As competitive antagonists at beta adrenergic receptors, the function of beta blockers is partially dependent on the presence of a beta agonist to antagonize, which is why their effectiveness can be altered by mutations in presynaptic α_2 receptors. For example, the α_{2A} Lys251 allele is found in 4% of African-Americans and 0.4% of Caucasians, and has been shown in functional studies to result in a 50% increase in function[21]. This mutation results in decreased norepinephrine release compared to the more common α_{2A} Asn251 allele, which could potentially lead to an exaggerated beta blocker response. In contrast, approximately 40% of African-Americans and 3% of Caucasians have an α_{2C} receptor coding polymorphism that results in a 12 nucleotide in-frame deletion, which results in nearly complete loss of function[22]. This α_{2C} Del322-325 polymorphism is associated with increased norepinephrine in the cardiac presynaptic cleft, which significantly diminishes the antagonistic effects of beta blockers, and has been shown to increase overall risk of heart failure and to significantly reduce the survival benefit of beta blockers in heart failure patients[23].

In addition to the genetic polymorphisms that alter the molecular function of adrenergic receptors themselves, polymorphisms in the genes which code for the enzymes involved in the metabolism of beta blockers can also affect the pharmacokinetics and ultimately the physiologic effects of beta blocker therapy. The hepatic cytochrome P450 2D6 (CYP2D6) enzyme, in particular, is responsible for phase-1 metabolism of most beta-blockers including metoprolol, carvedilol, propranalol, and labetalol, and has almost 100 known variants in the human population. These variants are grossly classified into 4 groups: ultra-rapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers[24]. Studies have demonstrated an increased risk of developing bradycardia and hypotension in patients with CYP2D6 poor metabolizer phenotypes who were treated with metoprolol[25]. Furthermore, the use of beta-blockers such as atenolol which are not metabolized by the CYP2D6 enzyme is associated with improved perioperative mortality outcomes[26].

Further studies will be needed in order to definitively characterize the impact of genetic variations on perioperative outcomes with respect to beta blockade. However, the current data suggest that numerous polymorphisms could affect the efficacy and potential side effect profile of beta blockers. As genetic testing becomes cheaper, and as our understanding of these genetic features develops, we may someday be able to screen high-risk individuals for particular genetic make-ups in order to determine the optimum pharmacologic strategy for preventing adverse perioperative cardiac events.

Precision Medicine in the Perioperative Period: Opioids

Another area where anesthesiologists may be able to use precision medicine to improve outcomes involves the use of opioid therapy in the perioperative setting. Independent predictors of postoperative pain include preoperative pain, preoperative anxiety, age, surgical procedure, and preoperative pain threshold and tolerance levels as measured by quantitative sensory testing[27]. However, despite the utilization of common anesthetic strategies 20%-40% of patients still report severe postoperative pain, and 5% go on to develop severe persistent pain that leads to some level of chronic disability[28]. Opioids remain the mainstay of postoperative analgesia, and are used in 72% of surgical cases. Moreover, opioid doses required to achieve adequate postoperative analgesia can vary as much as 40-fold, and have traditionally been difficult to predict[29]. Furthermore, liberal opioid use is constrained by a considerable side effect profile that notably includes sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression[30].

Much like the genetic variations that can affect the physiology of beta-blockade, genetic variations that affect a patient's response to opioid therapy include mutations in the genes that code for individual opioid receptors as well as mutations in genes that code for the enzymes involved in the metabolism of various opioids, although the perception of pain is further complicated by modulation of nociceptive inputs within the brainstem and cortical circuits[31]. For example, the analgesic efficacy of drugs that act on the mu-opioid receptor has been linked to a single nucleotide polymorphism at position 118 of the opioid receptor mu 1 (OPRM1) gene,

which encodes the mu-1 receptor. The frequency of the variant G allele varies from 10% to 48% depending on the population, with overall genotype frequencies of 31.3% for the AA allele, 58.3% for the AG allele, and 10.4% for the GG allele having been reported[32]. Specifically, the GG genotype has been shown to be associated with much higher opioid requirements to achieve postoperative pain relief, as well as chronic cancer pain relief[33]. Similarly, a study on intrathecal opioid analgesia showed improved response to intrathecal fentanyl in parturients with the OPRM1 304 G allele[34]. Variations in the opioid receptor kappa 1 (OPRK1) gene, which codes for the kappa-opioid receptor, have also been associated with variations in postoperative and chronic pain levels[35]. Interestingly, mutations in OPRM1, OPRK1, and opioid receptor delta 1 genes have also been associated with alcohol and opioid abuse and addiction[36,37].

Enzymes directly involved in the metabolism of opioids include phase-1 oxidation enzymes from the P450 family, such as CYP2D6, phase-2 conjugation enzymes such as uridine diphosphate glucuronyltransferase (UGT), and phase-3 membrane transporters, such as multidrug resistance protein (MDR1)[38]. The CYP2D6 enzyme is responsible for the biotransformation of codeine into morphine and hydrocodone into hydromorphone, both of which are far more potent than their parent compounds. Patients who fall into the CYP2D6 ultra metabolizers group can have dangerously high levels of morphine after standard doses of codeine[39], and patients identified as extensive metabolizers have improved pain relief from hydrocodone compared to poor metabolizers and extensive metabolizers who are pretreated with a CYP2D6 inhibitor[40]. The UGT2B7 enzyme metabolizes morphine into both morphine-6-glucuronide, a potent analgesic, and morphine-3-glucuronide that is associated with opioid-induced hyperalgesia, the UGT2B7-840G allele in particular is associated with reduced glucuronidation of morphine and highly variable hepatic clearance[41]. Lastly, mutations in the MDR1 protein, which codes for a membrane transporter found in the liver, have also been associated with various degrees of opioid responsiveness and adverse drug reactions. Specifically, the 3435C>T mutation decreases transporter function and is associated with increased respiratory depression from fentanyl[42], and combining this genotype with the OPRM1 A80G single nucleotide polymorphism allows detection of response to morphine therapy (strong responders, intermediate responders, and non-responders) with close to 100% sensitivity and 70% specificity[43].

Other genes that are not directly involved in the metabolism of opioids can still affect postoperative pain levels and associated opioid requirements. For example, catechol-O-methyl transferase (COMT) is primarily involved in catecholamine metabolism, but patients who are homozygous for the COMT-Val158Met polymorphism show a diminished mu-opioid mediated response to pain and a decreased morphine requirement for analgesia[42]. Another gene, calcium voltage-gated channel subunit alpha 2 delta 2, encodes a voltage dependent calcium channel that interacts with the G-protein of the mu-opioid receptor, the GG allele of which is found more frequently in patients with a high sensitivity to remifentanil[44]. Patients with SA/SA and SA/LG genotypes of the serotonin transporter also experience improved analgesic response to remifentanil compared to those with the LA/LA genotype[45].

Conclusions

The clinical implications of genetic variability in the perioperative setting are significant and under-recognized, owing largely to our limited historical capacity for mapping a patient's individual genetic profile. However, recent developments in gene sequencing technology have allowed greater access to genetic testing across a multitude of medical fields, and are facilitating the application of precision medicine to more disease processes than ever before. Inclusion of genetic testing as part of a patient's preoperative workup would allow anesthesiologists to select therapies that are tailored to each individual patient in order to optimize therapeutic efficacy and limit adverse drug reactions. For example, a patient with an elevated cardiac risk who also expresses a CYP2D6 poor metabolizer phenotype may benefit from beta blockade with atenolol, which is not metabolized by CYP2D6, rather than metoprolol in order to reduce the risk of bradycardia and hypotension. High risk patients with the α_{2A}Lys251 allele might benefit from low dose beta blockers; whereas high risk patients with the β_1Arg389 polymorphism might be expected to respond well to standard beta blockers at standard doses. Similarly, the presence of the OPRM1 GG genotype might be used to predict postoperative narcotic needs with the expectation that standard narcotic doses might be insufficient to achieve adequate analgesia. Further studies will be needed to test these hypotheses, and to determine the effects these genetic variables might have on perioperative outcomes. Moreover, further pharmacogenomic studies will be needed in order to identify other genes that might play a role in the pharmacodynamics and pharmacokinetics of common perioperative drugs. Genetic testing is still relatively expensive and must be weighed against the incidence and overall cost of adverse perioperative outcomes that might be avoided

with appropriate preoperative testing. However, we will eventually come to a point when we no longer ask ourselves whether we can afford to use precision medicine to guide perioperative therapies, but rather whether we can afford not to. Anesthesiologists and perioperative care providers shall learn the knowledge and be prepared to practice precision medicine to improve the outcome of our patients. Precision medicine is not far away from us. It is just with us.

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